

isopropoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.93 (d, 1H, J= 3.0 Hz), 7.47 (d, 2H, J= 9.3 Hz), 7.42 (t, 1H, J= 1.8 Hz), 7.17 (t, 1H, J= 8.1 Hz), 7.10 (bs, 1H), 7.00 (dd, 1H, J= 1.8 and 9.3 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.80 (d, 1H, J= 1.8 Hz), 6.58 (bs, 1H), 6.50 (dd, 1H, J= 1.5 and 8.1 Hz), 4.51 (2q, 1H, J= 5.7 Hz), 4.44 (s, 2H), 2.88 (d, 3H, J= 4.5 Hz), 1.33 (d, 6H, J= 5.7 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>): - 47198; LCMS: ret. time: 19.66 min.; purity: 97 %; MS (m/e): 426 (MH<sup>+</sup>).

**7.3.508 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R945170)**

In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)methyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(4-cyanomethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.91 (d, J= 5.1 Hz, 3H), 4.48 (s, 2H), 6.61 (ddd, J= 0.9, 2.7 and 8.1 Hz, 1H), 6.63 (br, 1H), 6.76 (d, J= 3.0 Hz, 1H), 6.84-6.89 (m, 4H), 7.18 (t, J= 8.1 Hz, 1H), 7.44 (d, J= 8.7 Hz, 2H), 7.51 (t, J= 2.1 Hz, 1H), 7.92 (d, 1H); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -167.70; LCMS: ret. time: 14.32 min.; purity: 100%; MS (m/e): 383.98 (MH<sup>+</sup>).

**7.3.509 5-Fluoro-N4-(3-isopropoxyphenyl)-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926489)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-isopropoxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidineamine with morpholine gave 5-fluoro-N4-(3-isopropoxyphenyl)-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.01 (d, 1H, J= 1.2 Hz), 7.95 (bs, 1H), 7.43-7.38 (m, 2H), 7.29 (s, 1H), 7.25-7.11 (m, 4H), 6.97 (bs, 1H), 6.73 (m, 1H), 6.67 (bdd, 1H), 4.48 (sept, 1H, J= 5.7 Hz), 3.87 (m, 4H), 3.79 (m, 4H), 1.30 (d, 6H, J= 5.7 Hz), LCMS: ret. time: 22.12 min.; purity: 98%; MS (m/e): 492 (MH<sup>+</sup>).

**7.3.510 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926772)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine with piperazine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.91 (d, 1H, J= 3.6 Hz), 7.42 (t, 1H, J= 2.4 Hz), 7.20-7.07 (m, 5H), 6.55 (m, 2H), 4.63 (s, 2H), 3.54 (t, 2H, J= 6 Hz), 3.40 (t, 2H, J= 5.1 Hz), 2.76 (t, 4H, J= 5.4 Hz); LCMS: ret. time: 12.98 min.; purity: 92%; MS (m/e): 439 (MH<sup>+</sup>).

**7.3.511 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926506)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with 2-hydroxyethylamine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.95 min.; purity: 96%; MS (m/e): 414 (MH<sup>+</sup>).

**7.3.512 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926508)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-ethoxy or methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with methylamine hydrochloride gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.64 (bs, 1H), 9.58 (bs, 1H), 8.15 (d, 1H, J= 4.2 Hz), 7.95 (bd, 1H), 7.25 (bd, 2H, J= 6.6 Hz), 7.16-7.07 (m, 4H), 6.53 (m, 2H), 4.35 (s, 2H), 2.64 and 2.62 (2s, 3H); LCMS: ret. time: 15.66 min.; purity: 98%; MS (m/e): 384 (MH<sup>+</sup>).

**7.3.513 5-Fluoro-N4-[3,4-(1,1,2,2-tetrafluoroethylenedioxy)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926732)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[3,4-(1,1,2,2-tetrafluoroethylenedioxy)phenyl]-4-pyrimidineamine and methylamine hydrochloride were reacted to yield 5-fluoro-N4-[3,4-(1,1,2,2-tetrafluoroethylenedioxy)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.65 (s, 1H), 9.37 (s, 1H), 8.16 (d, 1H, J= 3.6 Hz), 8.14 (d, 1H, J= 2.4 Hz), 7.97 (d, 1H, J= 4.8 Hz), 7.65 (dd, 1H, J= 2.4 and 8.7 Hz), 7.41 (d, 1H, J= 9.3 Hz), 7.34 (t, 1H, J= 2.4 Hz), 7.27 (d, 1H, J= 8.1 Hz), 7.13 (t, 1H, J= 8.1 Hz), 6.51 (dd, 1H, J= 2.1 and 7.5 Hz), 4.36 (s, 2H), 2.63 (d, 3H, J= 4.8 Hz); <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): - 25765 (pent, 2F), - 25830 (pent, 2F), - 46309; LCMS: ret. time: 24.85 min.; purity: 95 %; MS (m/e): 497 (MH<sup>+</sup>).

**7.3.514 N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R940254)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,5-dimethyl-4-hydroxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with morpholine gave N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-(N-morpholinocarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 18.38 min.; purity: 92 %; MS (m/e): 468 (MH<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.20 (1H, s), 9.10 (1H, s), 8.15 (1H, s), 8.11 (1H, d, J= 3.9 Hz), 7.43 (1H, d, J= 8.1 Hz), 7.32 (3H, m), 7.14 (1H, t, J= 8.1 Hz), 6.54 (1H, dd, J= 8.1 and 2.0 Hz), 4.77 (2H, s), 3.64 (4H, m), 3.54-3.45 (4H, m), 2.24 (6H, s).

**7.3.515 N4-(3-*tert*-Butylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R940276)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3-*tert*-butylphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with methylamine hydrochloride gave N4-(3-*tert*-butylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS:

ret. time: 22.90 min.; purity: 99 %; MS (m/e): 424 (MH<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.46 (1H, s), 9.34 (1H, s), 8.08 (1H, d, J= 3.9 Hz), 7.90 (1H, m), 7.30 (1H, d, J= 8.1 Hz), 7.46 (1H, m), 7.26 (1H, m), 7.20 (2H, m), 7.10-7.03 (2H, m), 6.47 (1H, d, J= 8.1 Hz), 4.26 (2H, s), 2.59 (3H, d, J= 4.5 Hz), 1.20 (9H, s).

5                                **7.3.516    N4-(3-*tert*-Butylphenyl)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R940277)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3-*tert*-butylphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with 2,3-dihydroxypropylamine gave N4-(3-*tert*-butylphenyl)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: retn. time: 20.46 min.; purity: 100 %; MS (m/e): 484 (MH<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.38 (1H, s), 9.29 (1H, s), 8.20 (1H, d, J= 3.9 Hz), 8.00 (1H, d, J= 8.3 Hz), 7.93 (1H, t, J= 5.5 Hz), 7.60 (1H, m), 7.47 (1H, m), 7.41-7.17 (4H, m), 6.59 (1H, dd, J= 8.3 and 2 Hz), 3.43 (2H, s), 3.39 (4H, m), 3.16 (1H, m), 1.36 (9H, s).

**7.3.517    N4-(3,3-Dihydroisobenzofuran-1-one-6-yl)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine R940293**

20                                In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[3-(ethoxycarbonylmethyleneoxy)phenyl]-N4-(3,3-dihydroisobenzofuran-1-one-6-yl)-5-fluoro-2,4-pyrimidinediamine and 3-amino-1,2-propanediol were reacted to N4-(3,3-dihydroisobenzofuran-1-one-6-yl)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.92 min.; purity: 92 %; MS (m/e): 483 (M<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.80 (1H, s), 9.46 (1H, s), 8.37-8.27 (2H, m), 8.21 (1H, s), 7.96 (1H, t, J= 4.6Hz), 7.24 (1H, d, J= 9Hz), 7.44 (1H, s), 7.37 (1H, d, J= 9 Hz), 7.23 (1H, t, J= 8 Hz), 6.60 (1H, dd, J= 7 and 3.75 Hz) 5.49 (2H, s), 4.46 (2H, s), 3.38 (4H, m), 3.2-3.1 (1H, m).

**7.3.518 N4-(3,4-Dimethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926733)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-dimethoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(3,4-dimethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.95 (d, 1H, J= 3.6 Hz), 7.45 (t, 1H, J= 1.8 Hz), 7.21-7.17 (m, 2H), 7.05 (dd, 1H, J= 2.7 and 8.7 Hz), 6.96-6.90 (m, 2H), 6.87 (d, 1H, J= 9.0 Hz), 6.72 (d, 1H, J= 2.4 Hz), 6.67-6.58 (m, 1H), 6.52 (dd, 1H, J= 3.6 and 8.1 Hz), 4.39 (s, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 2.90 (d, 3H, J= 4.8 Hz); LCMS: ret. time: 17.09 min.; purity: 98 %; MS (m/e): 428 (MH<sup>+</sup>).

**7.3.519 N2-[3-(N-2,3-Dihydroxypropylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926734)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-dimethoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 3-amino-1,2-propanediol were reacted to yield N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.05 (d, 1H, J= 4.2 Hz), 7.38-7.34 (m, 2H), 7.31-7.26 (m, 2H), 7.07 (t, 1H, J= 8.4 Hz), 6.89 (d, 1H, J= 8.7 Hz), 6.46 (dd, 1H, J= 2.4 and 8.4 Hz), 4.36 (s, 2H), 3.72 (s, 3H), 3.68 (s, 3H), 3.32-3.24 (m, 3H), 3.03 (dd, 1H, J= 6.9 and 13.5 Hz); <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): - 46574; LCMS: ret. time: 14.85 min.; purity: 94 %; MS (m/e): 488 (MH<sup>+</sup>).

**7.3.520 5-Fluoro-N4-(3-methoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926738)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-methoxyphenyl)-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield 5-fluoro-N4-(3-

methoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 18.40 min.; purity: 98 %; MS (m/e): 398 (MH<sup>+</sup>).

5                    **7.3.521    N2-[3-(N-2,3-Dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(3-methoxyphenyl)-2,4-pyrimidinediamine (R926739)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(3-methoxyphenyl)-2,4-pyrimidinediamine and 3-amino-1,2-propanediol were reacted to yield N2-[3-(N-2,3-

10                    dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(3-methoxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 16.66 min.; purity: 99 %; MS (m/e): 458 (MH<sup>+</sup>).

**7.3.522    N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R945140)**

15                    In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and piperazine gave N4-(3,5-dimethyl-4-

20                    hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 2.18 (s, 6H), 2.72 (q, J= 5.1 Hz, 4H), 3.32 (t, 2H), 3.52 (t, J= 5.1 Hz, 2H), 4.55 (s, 2H), 6.56 (ddd, J= 1.2, 2.4 and 8.1 Hz, 1 H), 7.03 (ddd, J= 1.2, 1.8 and 8.1 Hz, 1H), 7.11 (t, J= 8.1 Hz, 1H), 7.20 (s, 2H), 7.35 (t, J= 2.1 Hz, 1H), 7.84 (d, J= 3.9 Hz, 1H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): δ - 168.78; LCMS: ret. time: 14.32 min.; purity: 88.37%; MS (m/e): 467.06 (MH<sup>+</sup>).

25                    **7.3.523    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926488)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-

30                    fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with morpholine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.19 (t, 1H, J= 1.5 Hz), 7.90 (d, 1H, J= 3.9 Hz), 7.44 (d, 2H, J= 0.9 hz), 7.28 (s, 1H), 7.21 (t, 1H,

J= 2.4 Hz), 7.15 (t, 1H, J= 7.5 Hz), 7.08 (m, 1H), 7.61 (bd, 1H, J= 6.9 Hz), 3.8 (m, 4H), 3.65 (m, 4H); LCMS: ret. time: 17.21 min.; purity: 83%; MS (m/e): 450 (MH<sup>+</sup>).

5                    **7.3.524    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926493)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with methylamine hydrochloride gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.71 (d, 1H, J= 4.8 Hz), 8.00-7.92 (m, 2H), 7.56-7.52 (m, 1H), 7.44-7.39 (m, 2H), 7.12 (m, 2H), 6.69 (bdd, 1H), 2.96 and 2.94 (2s, 3H).

15                    **7.3.525    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-2-hydroxyethylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926497)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with 2-hydroxyethylamine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-2-hydroxyethylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.18 (d, 1H, J= 1.8 Hz), 7.80 (bs, 1H), 7.60 (m, 1H), 7.34-7.16 (m, 3H), 7.10 9t, 1H, 8.4 Hz), 6.85 (bdd, 1H), 6.62 (dd, 1H, J= 1.5 and 8.1 Hz), 3.70 (t, 2H, J= 4.8 Hz), 3.52 (t, 2H, J= 4.0 Hz); LCMS: ret. time: 14.49 min.; purity: 97%; MS (m/e): 424 (MH<sup>+</sup>).

25                    **7.3.526    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926500)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with piperazine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.19 (t, 1H, J= 1.2 Hz), 7.90 (d, 1H, J= 3.9 Hz), 7.43 (d, 2H, J= 1.2 Hz), 7.25-7.06 (m, 4H), 6.59

(m, 1H), 3.80 (m, 4H), 2.95 (m, 4H); LCMS: ret. time: 12.97 min.; purity: 79%; MS (m/e): 449 (MH<sup>+</sup>).

5                   **7.3.527    5-Cyano-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925844)**

                  In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-N-methylaminocarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-cyano-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine with methylamine hydrochloride gave 5-cyano-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 18.83 min.; purity: 96 %; MS (m/e): 391 (MH<sup>+</sup>).

**7.3.528    5-Cyano- N4-[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925845)**

15               In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-cyano-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine reacted with cyclopropylmethylamine to give 5-cyano-N4-[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 22.47 min.; purity: 100 %; MS (m/e): 431 (MH<sup>+</sup>).

**7.3.529    5-Cyano-N4-(3-hydroxyphenyl)-N2-[4-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925846)**

25               In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-cyano-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine reacted with 2,3-dihydroxypropylamine to give 5-cyano-N4-(3-hydroxyphenyl)-N2-[4-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.84 min.; purity: 100 %; MS (m/e): 451 (MH<sup>+</sup>).



**7.3.530 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-trifluoromethylphenyl)-2,4-pyrimidinediamine**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-N4-(3-trifluoromethylphenyl)-2,4-pyrimidineamine with methylamine hydrochloride gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-trifluoromethylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 21.98 min., purity: 86%, MS (m/e): 436 (MH<sup>+</sup>).

**7.3.531 N4-[4-(4,5-Dichloro-1H-imidazol-1-ylphenyl)]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926812)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N-4-[4-(4,5-dichloro-1H-imidazol-1-ylphenyl)]-5-fluoro-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with methylamine hydrochloride gave N4-[4-(4,5-dichloro-1H-imidazol-1-ylphenyl)]-5-fluoro N2-(3-[N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 21.02 min., purity: 100%, MS (m/e): 502 (MH<sup>+</sup>).

**7.3.532 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-methylaminocarbonyllindol-7-yl)- 2,4-pyridinediamine (R926815)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-N4-(3-trifluorophenyl)-2,4-pyrimidineamine with methylamine hydrochloride gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-methylaminocarbonyllindol-7-yl)- 2,4-pyridinediamine. LCMS: ret. time: 17.97 min., purity: 97%, MS (m/e): 435 (MH<sup>+</sup>).

**7.3.533 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926484)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-

(3-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and morpholine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.94 (bs, 1H), 7.35 (t, 1H, J= 2.4 Hz), 7.24 (m, 1H), 7.19 (t, 1H, J= 8.1 Hz), 7.10 (bdd, 1H, J= 6.9 Hz), 6.95 (m, 2H), 6.85 (d, 1H, J= 8.1 Hz), 6.94 (s, 1H), 6.58 (dd, 1H, J= 1.8 and 2.8 Hz), 4.64 (s, 2H), 4.27 9s, 4H), 3.62 (m, 4H), 3.55 (m, 4H); LCMS: ret. time: 18.45 min.; purity: 100%; MS (m/e): 482 (MH<sup>+</sup>).

**7.3.534 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926492)**

In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with morpholine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.27 (s, 1H), 9.17 (s, 1H), 8.14 (d, 1H, J= 2.4 Hz), 8.05 (d, 1H, J= 5.6 Hz), 7.58-7.46 (m, 2H), 7.27 (m, 1H), 7.15 (dd, 1H, J= 2.4 and 9 Hz), 6.80 9m, 1H), 4.24 (s, 4H), 3.80-3.45 (m, 8H); LCMS: ret. time: 19.97 min.; purity: 76%; MS (m/e): 492 (MH<sup>+</sup>).

**7.3.535 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926496)**

In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and methylamine hydrochloride gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.06 (s, 1H), 7.85 (d, 1H, J= 3.3 Hz), 7.42 (d, 2H, J= 1.2 Hz), 7.35 (s, 1H), 7.29 (d, 1H, J= 2.4 Hz), 6.99 (dd, 1H, J= 3.3 and 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 4.24 (s, 4H), 2.94 (s, 3H); LCMS: ret. time: 18.05 min.; purity: 99%; MS (m/e): 436 (MH<sup>+</sup>).

**7.3.536 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-2-hydroxyethylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926498)**

In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with 2-hydroxyethylamine yielded N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-2-hydroxyethylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.07 (d, 1H, J= 1.2 Hz), 7.86 (d, 1H, J= 3.9 Hz), 7.43 (d, 2H, J= 1.5 Hz), 7.38 (s, 1H), 7.29 (d, 1H, J= 2.4 Hz), 6.98 (dd, 1H, J= 2.1 and 9 Hz), 6.78 (d, 1H, J= 8.7 Hz), 4.23 (s, 4H), 3.72 (t, 2H, J= 5.7 Hz), 3.53 (t, 2H, J= 6.0 Hz); LCMS: ret. time: 16.21 min.; purity: 97%; MS (m/e): 466 (MH<sup>+</sup>).

**7.3.537 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926499)**

In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and piperazine yielded N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.26 (s, 1H), 9.16 (s, 1H), 8.12 (d, 1H, J= 1.8 Hz), 8.04 (d, 1H, J= 3.6 Hz), 7.49 (d, 2H), 7.30 (d, 1H, J= 2.4 Hz), 7.20 (s, 1H), 7.15 (bdd, 1H, J= 3 Hz), 6.79 (d, 1H, J= 8.7 Hz), 4.22 (s, 4H), 2.48 (s, 3H); LCMS: ret. time: 14.61 min.; purity: 94%; MS (m/e): 491 (MH<sup>+</sup>).

**7.3.538 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926503)**

In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and piperazine were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 9.14 (bs, 2H), 8.04 (d, 3.6 Hz), 7.32-7.20 (m, 4H), 7.06 (t, 1H, J= 8.1

Hz), 6.79 (d, d, 1H, J= 9 Hz), 6.43 (bd, 1H, J= 9.9 Hz), 4.64 (s, 2H), 4.20 (bs, 4H), 3.29 (m, 4H), 2.59 (m, 4H); LCMS: ret. time: 14.92 min.; purity: 99%; MS (m/e): 481 (MH<sup>+</sup>).

5                    **7.3.539    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxy-1,1-dimethylethylamino)carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine (R926764)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 2-amino-2-methylpropanol gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxy-1,1-dimethylethylamino)carboxymethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.95 (d, 1H, J= 2.7 Hz), 7.47 (t, 1H, J= 2.4 Hz), 7.20 (t, 1H, J= 8.1 Hz), 7.03 (dd, 1H, J= 1.2 and 8.1 Hz), 6.98 (dd, 1H, J= 3 and 8.2 Hz), 6.93 (s, 1H), 6.84 (d, 1H, J= 8.7 Hz), 6.66 (d, 1H, J= 3 Hz), 6.57 (bs, 1H), 6.53 (m, 1H), 4.65 (m, 1H), 4.39 (s, 2H), 4.28 (s, 4H), 3.63 (d, 2H, J= 5.7 Hz), 1.31 (s, 6H); LCMS: ret. time: 19.19 min.; purity: 89%; MS (m/e): 484 (MH<sup>+</sup>).

**7.3.540    N2-[3-(N-Cyclohexylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926765)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and cyclohexylamine gave N2-[3-(N-cyclohexylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.94 (d, 1H, J= 3.3 Hz), 7.41 (t, 1H, J= 2.4 Hz), 7.28 (d, 1H, J= 2.4 Hz), 7.20 (t, 1H, J= 7.5 Hz), 7.04 (dd, 1H, J= 1.2 and 8.1 Hz), 6.95 (m, 2H), 6.85 (d, 1H, J= 8.7 Hz), 6.68 (d, 1H, J= 3.0 Hz), 6.53 (dd, 1H, J= 2.4 and 8.4 Hz), 6.45 (bd, 1H, J= 8.1 Hz), 4.43 (s, 2H), 4.24 (s, 4H), 3.85 (m, 1H), 1.90 (m, 2H), 1.75-1.55 (m, 2H), 1.45-1.05 (m, 6H); LCMS: ret. time: 23.70 min.; purity: 97%; MS (m/e): 494 (MH<sup>+</sup>).

30                    **7.3.541    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[N-methyl-N-(2-hydroxyethyl)amino]carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926766)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-

ethylenedioxyphenyl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and N-methyl-N-2-hydroxyethylamine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[N-methyl-N-(2-hydroxyethyl)amino]carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.93 (d, 1H, J= 3 Hz), 7.92 (bs, 1H), 7.35 (t, 1H, J= 2.4 Hz), 7.18 (m, 1H), 7.06 (dd, 1H, J= 1.2 and 8.7 Hz), 6.97 (t, 1H, J= 2.4 Hz), 6.94 (m, 1H), 6.85 (d, 1H, J= 8.7 Hz), 6.70 (bd, 1H), 6.59 (dd, 1H, J= 1.8 and 8.1 Hz), 4.66 (s, 2H), 4.28 (s, 4H), 3.79 (t, 2H, J= 5.4 Hz), 3.56 (t, 3H, J= 5.4 Hz), 3.10 (s, 3H); LCMS: ret. time: 16.64 min.; purity: 97%; MS (m/e): 470 (MH<sup>+</sup>).

**7.3.542 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926767)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and homopiperazine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-homopiperazinocarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.27 (s, 1H), 9.17 (d, 1H, J= 1.2 Hz), 8.14 (s, 1H), 8.05 (d, 1H, J= 3.6 Hz), 7.54-7.46 (m, 2H), 7.30 (d, 1H, J= 2.4 Hz), 7.24 (s, 1H), 7.17 (dd, 1H, J= 2.4 and 8.7 Hz), 6.80 (d, 1H, J= 8.7 Hz), 4.22 (s, 4H), 3.79 (m, 2H), 3.65 (m, 2H), 3.01 (m, 2H), 2.89 (m, 2H), 1.90 (m, 1H), 1.80 (m, 1H); <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): - 46687; LCMS: ret. time: 14.99 min.; purity: 77%; MS (m/e): 505 (MH<sup>+</sup>).

**7.3.543 N4-(3,4-Ethylenedioxyphenyl)-N2-[3-(N,N-dimethylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R925755)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and N,N-dimethylamine hydrochloride gave N4-(3,4-ethylenedioxyphenyl)-N2-[3-(N,N-dimethylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.16 (d, 1H, J= 1.2 Hz), 9.15 (s, 1H), 8.04 (d, 1H, J= 5.6 Hz), 7.30-7.21 (m, 4H), 7.06 (t, 1H, J= 9Hz), 6.78 (d, 1H, J= 9Hz), 6.43 (m, 1H), 4.65 (s, 2H), 4.21 (s, 4H), 2.94 (s, 3H), 2.82 (s, 3H); LCMS: ret. time: 18.70 min.; purity: 83%; MS (m/e): 440 (MH<sup>+</sup>).

**7.3.544 N2-[3-[N,N-Bis-(2-hydroxyethylamino)]  
carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-  
5-fluoro-2,4-pyrimidinediamine (R926781)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and N,N-bis(hydroxyethyl)amine gave N2-[3-[N,N-bis-(2-hydroxyethylamino)]carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.86 (d, 1H, J= 3.6 Hz), 7.25 (m, 2H), 7.17-7.03 (m, 3H), 6.78 (d, 1H, J= 9Hz), 6.58 (bd, 1H), 4.80 (s, 2H), 4.23 (s, 4H), 3.71 (t, 4H, J= 4.8 Hz), 3.53 (t, 2H, J= 6Hz), 3.49 (t, 3H, J= 5.4 Hz); LCMS: ret. time: 16.25 min.; purity: 94%; MS (m/e): 500 (MH<sup>+</sup>).

**7.3.545 N2-[3-(N-2,3-Dihydroxypropylamino)  
carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-  
5-fluoro-2,4-pyrimidinediamine (R926782)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and 2,3-dihydroxypropylamine gave N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.86 (d, 1H, J= 4.2 Hz), 7.37 (t, 1H, J= 1.8 Hz), 7.24 (d, 1H, J= 2.4 Hz), 7.14 (m, 2H), 7.09 (dd, 1H, J= 2.4 and 9 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.59 (m, 1H), 4.39 (s, 2H), 4.22 (s, 4H), 3.73 (m, 1H), 3.48 (m, 4H); <sup>19</sup>F NMR (CD<sub>3</sub>OD): - 47575; LCMS: ret. time: 15.97; purity: 98%; MS (m/e): 486 (MH<sup>+</sup>).

**7.3.546 N2-[2-(N-2,3-Dihydroxypropylamino)carbonylbenzofuran-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926783)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and 2,3-dihydroxypropylamine gave N2-[2-(N-2,3-dihydroxypropylamino)carbonylbenzofuran-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.86 (d, 1H, J= 4.2 Hz), 7.35 (t, 1H, J= 1.2

Hz), 7.24 (d, 1H, J= 3 Hz), 7.15 (m, 2H), 7.07 (dd, 1H, J= 2.1 and 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.59 (m, 1H), 4.40 9s, 1H), 4.23 (s, 4H), 4.03 (t, 1H, J= 5.7 Hz), 3.67 (d, 2H, 3.6 Hz), 3.65 (d, 2H, J= 4.2 Hz);  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{OD}$ ): -47578; LCMS: ret. time: 15.72 min.; purity: 99%; MS (m/e): 486 ( $\text{MH}^+$ ).

5                    **7.3.547    N2-[3-(N-1,3-Dihydroxy-2-propylamino) carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926784)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 2-amino-1,3-propanediol gave N2-[3-(N-1,3-dihydroxy-2-propylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  8.08 (bd, 1H), 7.86 (bs, 1H), 7.44 (s, 2H), 7.39 (s, 1H), 7.29 (d, 1H, J= 2.4 Hz), 6.97 (dd, 1H, J= 2.4 and 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 4.24 (s, 4H), 3.84 (m, 1H), 3.56 (m, 2H), 3.44 (m, 2H); LCMS: ret. time: 16.63 min.; purity: 97%; MS (m/e): 496 ( $\text{MH}^+$ ).

**7.3.548    N2-[2-(N-1,3-Dihydroxy-2-propylamino)carbonylbenzofuran-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926785)**

20                    In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and 2-amino-1,3-propanediol gave N2-[2-(N-1,3-dihydroxy-2-propylamino)carbonylbenzofuran-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  8.08 (t, 1H, J= 1.8 Hz), 7.86 (d, 1H, J= 3.9 Hz), 7.45 (s, 2H), 7.41 (s, 1H), 7.29 (d, 1H, J= 2.4 Hz), 6.97 (dd, 1H, J= 3 and 8.7 Hz), 6.77 (d, 1H, J= 8.7 Hz), 4.24 (s, 4H), 4.19 (t, 1H, J= 5.7 Hz), 3.75 (d, 4H, J= 5.4 Hz);  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{OD}$ ): - 47745; LCMS: ret. time: 15.09 min., purity: 97%; MS (m/e): 496 ( $\text{MH}^+$ ).

30                    **7.3.549    N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R940265)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3-

chloro-4-hydroxy-5-methylphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with morpholine gave N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine.

LCMS: ret. time: 18.66 min.; purity: 92 %; MS (m/e): 487 ( $M^+$ ), 489 ( $MH^+$ );  $^1H$  NMR (DMSO- $d_6$ ): 9.28 (2H, s), 9.01 (1H, s), 8.17 (1H, d,  $J = 3.6$  Hz), 7.65 (1H, d,  $J = 2.4$  Hz), 7.5

(1H, d,  $J = 2.7$  Hz), 7.42 (1H, d,  $J = 6.6$  Hz), 7.29 (1H, s), 7.18 (1H, t,  $J = 8.1$  Hz), 6.57 (1H, dd,  $J = 6.6$  and  $2.2$  Hz), 4.79 (2H, s), 3.67 (4H, m), 3.52 (4H, m), 2.29 (3H, s).

**7.3.550 N4-(3,5-Dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950187)**

N4-(3,5-Dichlorophenyl-4-hydroxy)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (0.5 g, 1.1 mmol) was dissolved in EtOH:morpholine (4 ml : 4ml) and the mixture was refluxed for 1 day (100 °C oil-bath temperature). The mixture was cooled to 22 °C, diluted with water and brine, filtered, and dried under reduced pressure to give N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine.  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  9.35 (s, 1H), 9.22 (s, 1H), 8.09 (d, 1H,  $J = 3.6$  Hz), 7.94 (m, 1H), 7.75 (m, 1H), 7.27 (m, 1H), 7.18 (m, 1H), 7.12 (t, 1H,  $J = 8.4$  Hz), 6.44 (m, 1H), 4.64 (s, 2H), 3.39 (m, 4H), 2.68 (m, 4H); LCMS purity: 92.6%; MS (m/e): 507.89 ( $M^+$ , 100).

**7.3.551 N4-(3,5-Dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950188)**

In like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,5-dichloro-4-hydroxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine and piperazine were reacted to prepare N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.26 min.; purity: 88.5%; MS (m/e): 506.89 ( $MH^+$ ).

**7.3.552 N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926776)**

In like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3-



ethoxycarbonylmethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine with methylamine hydrochloride gave N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 16.94 min.; purity: 73%; MS (m/e): 426 (MH<sup>+</sup>).

5                                **7.3.553    N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-(4-methylaminocarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945173)**

In a manner analogous to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(4-methylaminocarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine, N4-(4-cyanomethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride salt gave N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(4-methylaminocarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (acetone-d<sub>6</sub>):  
 10                                δ 2.80 (d, 3H), 4.21-4.28 (m, 4H), 4.47 (s, 2H), 6.71 (d, J= 8.7 Hz, 1H), 6.96 (d, J= 9.0 Hz, 2H), 7.06 (dd, J= 2.7 and 9.0 Hz, 1H), 7.41 (d, J= 2.4 Hz, 1H), 7.74 (d, J= 9.0 Hz, 2H), 7.93  
 15                                (d, J= 3.6 Hz, 1H), 8.20 (br, 1H, NH), 8.41 (br, 1H, NH); <sup>19</sup>F NMR (282 MHz, acetone-d<sub>6</sub>): δ - 169.05; LCMS: ret. time: 17.47 min.; purity: 98.99%; MS (m/e): 425.89 (MH<sup>+</sup>).

**7.3.554    N2-[4-(2-N,N-Dimethylaminoethyl)oxyphenyl]-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R909253)**

20                                In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-4-pyrimidineamine and 4-(2-N,N-dimethylaminoethyl)oxyaniline were reacted to yield N2-[4-(2-N,N-dimethylaminoethyl)oxyphenyl]-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD):  
 25                                δ 8.0 (d, 1H J= 4 Hz), 7.42 (m, 2H), 7.24 (m, 2H), 7.05 (m, 2H), 6.85 (m, 1H), 4.39 (s, 2H), 4.30 (m, 2H), 3.66 (m, 2H), 3.04 (s, 6H), 2.83 (s, 3H); LCMS: ret. time: 14.0 min.; purity: 96 %; MS (m/e): 455 (MH<sup>+</sup>).

30                                **7.3.555    N2-(1,4-Benzoxazin-6-yl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R909247)**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-4-pyrimidineamine and 6-amino-1,4-benzoxazine were reacted to yield N2-(1,4-

benzoxazin-6-yl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H (DMSO-d<sub>6</sub>): δ 8.0 (d, 1H), 7.6 (m, 1H), 7.42 (m, 1H), 7.20 (m, 1H), 6.95 (m, 1H), 6.76 (m, 1H), 6.56 (m, 1H), 4.43 (s, 2H), 4.05 (m, 2H), 3.25 (s, 3H), 3.13 (m, 2H); LCMS: ret time: 17.67 min.; MS (m/e): 425 (MH<sup>+</sup>).

5                                **7.3.556    N2-(4-Dihydrobenzofuranyl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R909249)**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-4-pyrimidineamine and 5-amino-2,3-dihydrobenzofuran were reacted to yield  
10                                N2-(4-dihydrobenzofuranyl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.09 (d, 1H), 8.00 (m, 1H), 7.42 (m, 2H), 7.05 (m, 1H), 6.96 (m, 1H), 6.76 (m, 1H), 6.58 (m, 1H), 4.53 (m, 2H), 4.25 (s, 2H), 3.15 (m, 2H), 2.70 (m, 3H); LCMS: ret time: 19.24 min; MS (m/e): 410 (MH<sup>+</sup>).

15                                **7.3.557    N2-(3-*tert*-Butylphenyl)-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R940267)**

In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(3-*tert*-butylphenyl)-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with methylamine hydrochloride gave N2-(3-*tert*-butylphenyl)-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 22.22 min.; purity: 97 %; MS (m/e): 424 (MH<sup>+</sup>); <sup>1</sup>□□□□ (CDCl<sub>3</sub>): δ 7.98 (2H, m), 7.76 (2H, m), 7.56 (1H, t, J= 1.3 Hz), 7.28-7.22 (1H, m), 7.04 (1H, d, J= 7.8 Hz), 6.90  
25                                (1H, dd, J= 9 Hz, J= 1.3 Hz), 6.80 (1H, 2.6 Hz), 6.66 (1H, dd, J= 9 and 2.6 Hz), 6.46 (1H, s), 4.53 (2H, s), 2.88 (3H, d, J= 5.1 Hz), 1.31 (9H, s).

**7.3.558    N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926491)**

30                                In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(3,4-ethylenedioxyphenyl)-N4-(2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine with methylamine hydrochloride gave N2-(3,4-ethylenedioxyphenyl)-5-

fluoro-N4-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.10 (s, 1H), 7.94 (d, 1H, J= 5.1 Hz), 7.59 (s, 2H), 7.44 (s, 1H), 6.96 (d, 1H, J= 2.4 Hz), 6.82 (d, 1H, J= 8.4 Hz), 6.76 (dd, 1H, J= 3.6 and 8.1 Hz), 4.22 (s, 2H), 4.21 (s, 2H), 2.95 (s, 3H); LCMS: ret. time: 17.76 min.; purity: 97%; MS (m/e): 436 (MH<sup>+</sup>).

5                                    **7.3.559    N2-(3,5-Dimethoxyphenyl)-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R926810)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(3,5-dimethoxyphenyl)-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with methylamine hydrochloride gave N2-(3,5-dimethoxyphenyl)-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.93 (d, 1H, J= 3.9 Hz), 7.72 (t, 1H, J= 1.8 Hz), 7.27-7.19 9m, 2H), 6.88 (d, 2H, J= 2.4 Hz), 6.72 (m, 1H), 6.01 (t, 1H, J= 2.4 Hz), 4.44 (s, 2H), 3.67 (s, 6H), 2.80 (s, 3H).

**7.3.560    5-Bromo-N2-(3,4-ethylenedioxyphenyl)-N4-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925851)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-bromo-N2-(3,4-ethylenedioxyphenyl)-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield 5-bromo-N2-(3,4-ethylenedioxyphenyl)-N4-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.01 (s, 1H), 7.48 (d, 2H, J= 8.7 Hz), 7.09 (d, 1H, J= 3.0 Hz), 7.08 (d, 2H, J= 8.7 Hz), 6.81 (dd, 1H, J= 8.7 Hz), 6.64 (d, 1H, J= 8.7 Hz), 4.52 (s, 2H), 4.20 (bs, 4H), 2.83 (s, 3H); LCMS: ret. time: 19.13 min.; purity: 94 %; MS (m/e): 487 (MH<sup>+</sup>).

**7.3.561    N2-(3-Hydroxyphenyl)-5-trifluoromethyl-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926741)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(3-hydroxyphenyl)-5-trifluoromethyl-N4-(3-N-methoxycarbonylmethyleneoxyphenyl)-2,4-

pyrimidinediamine and methylamine hydrochloride were reacted to yield N2-(3-hydroxyphenyl)-5-trifluoromethyl-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 18.52 min.; purity: 96%; MS (m/e): 434 (MH<sup>+</sup>).

5                                **7.3.562    N2,N4-Bis[4-(N-n-butylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925860)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and n-butylamine were reacted to yield N2,N4-bis[4-(N-n-butylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.77 (bs, 1H), 9.38 (bs, 1H), 8.42 (s, 1H), 8.09 (t, 1H, J= 5.4 Hz), 8.02 (t, 1H, J= 5.7 Hz), 7.48-7.34 (m, 4H), 6.93 (d, 2H, J= 9.3 Hz), 6.82-6.72 (m, 2H), 4.47 (s, 2H), 4.38 (s, 2H), 3.14-3.06 (m, 4H), 1.42-1.33 (m, 4H), 1.28-1.18 (m, 4H), 0.83 (t, 6H, J= 6.9 Hz); LCMS: ret. time: 26.40 min.; purity: 97 %; MS (m/e): 546 (MH<sup>+</sup>).

15                                **7.3.563    N2,N4-Bis[4-(N-isopropylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925861)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and isopropylamine were reacted to yield N2,N4-bis[4-(N-isopropylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.41 (s, 1H), 7.90 (d, 1H, J= 7.5 Hz), 7.81 (d, 1H, J= 7.5 Hz), 7.50-7.36 (m, 4H), 6.93 (d, 2H, J= 8.7 Hz), 6.84-6.75 (m, 2H), 4.45 (s, 2H), 4.36 (s, 2H), 3.99-3.87 (m, 2H), 1.08 (d, 6H, J= 3.0 Hz), 1.06 (d, 25 6H, J= 2.4 Hz); LCMS: ret. time: 23.45 min.; purity: 89 %; MS (m/e): 518 (MH<sup>+</sup>).

**7.3.564    N2,N4-Bis[4-(N-n-propylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925853)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and n-propylamine were reacted to yield N2,N4-bis[4-(N-n-propylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.78 (bs, 1H), 9.38 (bs, 1H), 8.41.

(s, 1H), 8.07 (dt, 2H, J= 6.0 and 22.5 Hz), 7.48-7.36 (m, 4H), 6.93 (d, 2H, J= 8.7 Hz), 6.78 (d, 2H, J= 8.1 Hz), 4.48 (s, 2H), 4.39 (s, 2H), 3.07 (2q, 4H, J= 7.2 Hz), 1.47-1.38 (m, 4H), 0.90-0.77 (m, 6H); LCMS: ret. time: 23.67 min.; purity: 94 %; MS (m/e): 519 (MH<sup>+</sup>).

5                                **7.3.565    N2,N4-Bis[4-(N-morpholino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925854)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and morpholine were reacted to yield N2,N4-bis[4-(N-morpholino)carbonylmethyleneoxyphenyl]-5-cyano-  
10 2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.78 (bs, 1H), 9.31 (bs, 1H), 8.41 (s, 1H), 7.43 (d, 4H, J= 8.1 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.75 (d, 2H, J= 8.4 Hz), 4.84 (s, 2H), 4.74 (s, 2H), 3.76 (t, 4H, J= 5.1 Hz), 3.62-3.50 (m, 4H), 3.49-3.38 (m, 4H), 3.08-3.01 (m, 4H); LCMS: ret. time: 19.25 min.; purity: 89 %; MS (m/e): 574 MH<sup>+</sup>.

15                                **7.3.566    N2,N4-Bis[4-(N-piperidino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925855)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and piperidine were reacted to yield N2,N4-bis[4-(N-piperidino)carbonylmethyleneoxyphenyl]-5-cyano-  
20 2,4-pyrimidinediamine. <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 8.86 (bs, 1H), 8.48 (bs, 1H), 8.34 (s, 1H), 7.61-7.50 (m, 4H), 6.98 (d, 2H, J= 8.7 Hz), 6.90 (d, 2H, J= 9.3 Hz), 4.84 (s, 2H), 4.75 (s, 2H), 3.59-3.48 (m, 8H), 1.68-1.44 (m, 12H); LCMS: ret. time: 24.76 min.; purity: 98 %; MS (m/e): 571 (MH<sup>+</sup>).

25                                **7.3.567    N2,N4-Bis[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925859)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and  
30 cyclopropylmethylamine were reacted to yield N2,N4-bis[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.78 (bs, 1H), 9.36 (bs, 1H), 8.41 (s, 1H), 8.18 (t, 1H, J= 5.1 Hz),

8.10 (t, 1H, J= 5.1 Hz), 7.52-7.38 (m, 4H), 6.94 (d, 2H, J= 8.7 Hz), 6.84-6.76 (m, 2H), 4.48 (s, 2H), 4.40 (s, 2H), 3.00 (q, 4H, J= 6.3 Hz), 0.97-0.88 (m, 2H), 0.40-0.33 (m, 4H), 0.18-0.03 (m, 4H); <sup>19</sup>F NMR (CDCl<sub>3</sub>): LCMS: ret. time: 24.58 min.; purity: 100 %; MS (m/e): 543 (MH<sup>+</sup>).

5                                    **7.3.568    N4-(3-Aminophenyl)-N2-(1,4-benzoxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950254)**

N4-(3-Nitrophenyl)-N2-[(2H)1,4-benzoxazin-3(4H)-one-6-yl]-5-fluoro-2,4-pyrimidinediamine (940 mg, 2.5 mmol) and Pd/C 10% (300 mg, 50% water content) were suspended in EtOH (7 mL) and 10% aqueous HCl (5 mL) and hydrogenated in a Parr  
10                                    apparatus for 3 hours (22 °C, 60 psi). The suspension was filtered over celite and neutralized by addition of K<sub>2</sub>CO<sub>3</sub>. The solvents were removed and the resulting black slurry was suspended in MeOH. Silica gel (4 g) was added and the volatiles were removed under reduced pressure. The residue was subjected to column chromatography on silica gel (CHCl<sub>3</sub>-Acetone, 2:1) to give 186 mg of N4-(3-aminophenyl)-N2-(1,4-benzoxazin-6-yl)-5-  
15                                    fluoro-2,4-pyrimidinediamine as brownish solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.92 (s, 1H), 8.64 (s, 1H), 7.95 (d, 1H, J= 3.6 Hz), 7.11 (s, 1H), 6.84-6.95 (m, 3H), 6.66 (dd, 1H, J= 2.4, 9.0 Hz), 6.46 (d, 1H, J= 8.1 Hz), 6.28 (d, 1H, J= 8.1 Hz), 5.62 (s, 1H), 4.98 (s, 2H), 4.03 (m, 2H), 3.31 (m, 2H); LCMS purity: 98.4%; MS (m/e): 352.7 (M<sup>+</sup>, 100).

20                                    **7.3.569    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950200)**

N2-(3-Ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (50 mg, 0.11 mmol) was dissolved in EtOH:4-(2-aminoethyl)morpholine (0.5 ml : 0.5 ml) and the mixture was refluxed for 3 hours (100 °C  
25                                    oil-bath temperature). The mixture was cooled to 22 °C, diluted with water and washed with EtOAc. The organic phase was dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and the residue was subjected to column chromatography on silica gel (CHCl<sub>3</sub>:Acetone, 2:1) to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub> + CD<sub>3</sub>OD):  
30                                    δ 7.92 (d, 1H, J= 4.1 Hz), 7.31 (d, 1H, J= 2.3 Hz), 7.20 (dd, 1H, J= 2.7, 8.8 Hz), 6.87-6.99 (m, 2H), 6.74 (d, 1H, J= 8.8 Hz), 6.09 (m, 1H), 4.19 (m, 4H), 3.38 (m, 4H), 3.16 (t, 2H, J= 6.3 Hz), 2.28 (t, 2H, J= 6.3 Hz); LCMS purity: 99.2%; MS (m/e): 524.01 (M<sup>+</sup>, 100).

**7.3.570 N4-(3,4-Ethylenedioxyphenyl)-N2-[3-N-methylamino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950191)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,  
5 N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and methylamine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 17.32 min.; purity: 99.3%; MS (m/e): 425.04  
10 (MH<sup>+</sup>).

**7.3.571 N2-[3-(N-Amino)carbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950192)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,  
15 N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and aqueous ammonia were reacted to prepare N2-[3-(N-amino)carbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 16.59 min.; purity: 98.8%; MS (m/e): 411.02 (MH<sup>+</sup>).

**7.3.572 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950193)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,  
25 N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and morpholine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 18.70 min.; purity: 85.8%; MS (m/e): 481.05 (MH<sup>+</sup>).

**7.3.573 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-(N-methyl)-piperazino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950194)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,

N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N-methylpiperazine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-(N-methyl)piperazino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.75 min.; purity:

5 99.1%; MS (m/e): 494.06 (MH<sup>+</sup>).

**7.3.574 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethyleneamino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950195)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,  
10 N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and 2-aminoethanol were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethyleneamino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine.  
15 LCMS: ret. time: 16.23 min.; purity: 97.3%; MS (m/e): 455.02 (MH<sup>+</sup>).

**7.3.575 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)ethyleneaminocarbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950196)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,  
20 N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N-methyl-ethylen-1,2-diamine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)ethyleneaminocarbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.34 min.; purity:  
25 98.2%; MS (m/e): 468.06 (MH<sup>+</sup>).

**7.3.576 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950197)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,  
30 N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and piperazine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-



fluoro-N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 15.38 min.; purity: 93.2%; MS (m/e): 479.99 (MH<sup>+</sup>).

5                    **7.3.577    N2-[3-(N-Benzylamino)ethyleneaminocarbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950198)**

                  In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N-benzyl-ethylen-1,2-diamine were reacted to prepare N2-[3-(N-benzylamino)ethyleneaminocarbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 17.70 min.; purity: 92.5%; MS (m/e): 544.04 (MH<sup>+</sup>).

15                    **7.3.578    N2-[3-(N,N'-Bis(2-N-hydroxyethyl)amino)carbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950199)**

                  In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N,N'-bis(2-hydroxyethyl)amine were reacted to N2-[3-(N,N'-bis(2-N-hydroxyethyl)amino)carbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 15.81 min.; purity: 99.4%; MS (m/e): 499.01 (MH<sup>+</sup>).

25                    **7.3.579    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950217)**

                  In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and methylamine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.41 min.; purity: 93.0%; MS (m/e): 383.02 (MH<sup>+</sup>).

**7.3.580 N2-(3-Aminocarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950219)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,  
5 N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and aqueous ammonia were reacted to prepare N2-(3-aminocarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 14.23 min.; purity: 95.0%; MS (m/e): 369.03 (MH<sup>+</sup>).

**7.3.581 N2-[3-(N,N-Dimethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950220)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,  
N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and dimethylamine were reacted to prepare N2-[3-(N,N-dimethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 16.59 min.; purity: 96.5%; MS (m/e): 397.06 (MH<sup>+</sup>).

**7.3.582 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950221)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,  
N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and morpholine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 16.29 min.; purity: 91.5%; MS (m/e): 439.03 (MH<sup>+</sup>).

**7.3.583 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950222)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine,  
N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and piperazine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-

N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.04 min.; purity: 89.9%; MS (m/e): 438.06 (MH<sup>+</sup>).

5                   **7.3.584    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[N-(N-methyl)piperazino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950223)**

                  In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and N-methylpiperazine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[N-(N-methyl)piperazino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.06 min.; purity: 98.7%; MS (m/e): 452.06 (MH<sup>+</sup>).

**7.3.585    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950224)**

15                   In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and 2-aminoethanol were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.28 min.; purity: 97.3%; MS (m/e): 413.04 (MH<sup>+</sup>).

**7.3.586    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)ethylamino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950225)**

25                   In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and N-methyl-ethylen-1,2-diamine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)ethylamino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.31 min.; purity: 94.7%; MS (m/e): 426.01 (MH<sup>+</sup>).

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**7.3.587 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-2-morpholinoethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950226)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and N-morpholinylethylamine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-morpholinoethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.66 min.; MS (*m/e*): 482.39 (MH<sup>+</sup>).

**7.3.588 R935184: 5-Fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reacted with Me<sub>2</sub>NH.HCl and *i*-Pr<sub>2</sub>NEt in methanol to produce 5-fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 6.91 min.; purity: 98%; MS (*m/e*): 440 (MH<sup>+</sup>).

**7.3.589 R935196: N2-[3-(1-Bis(N-methylaminocarbonyl)ethoxy)phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidineamine:**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[3-(1-bis(ethyloxycarbonyl)ethoxy)phenyl]-5-fluoro-N2-[4-isopropoxyphenyl]-2,4-pyrimidinediamine was reacted with Me<sub>2</sub>NH.HCl and *i*-Pr<sub>2</sub>NEt in presence of methanol to produce N2-[3-(1-bis(N-methylaminocarbonyl)ethoxy)phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidineamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.18 (s, 1H), 9.15 (s, 1H), 8.07 (app qt, 2H, J= 4.7 Hz), 8.01 (d, 1H, J= 3.5 Hz), 7.65-7.62 (m 2H), 7.36 (br s, 1H), 7.28 (dd, 1H, J= 1.1 and 8.2 Hz), 7.03 (t, 1H, J= 8.2 Hz), 6.87 (d, 2H, J= 8.8 Hz), 6.35 (dd, 1H, J= 1.1 and 8.8 Hz), 4.54 (q, 1H, J= 6.4 Hz), 2.62 (d, 6H, J= 4.7 Hz), 1.49 (s, 3H), 1.23 (d, 6H, J= 5.8 Hz). LCMS: ret. time: 19.40 min.; purity: 94%; MS (*m/e*): 497 (MH<sup>+</sup>).

**7.3.590 R935202: 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine:**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reacted with Me<sub>2</sub>NH.HCl to give 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.21 (s, 1H), 9.19 (s, 1H), 8.06 (d, 1H, J= 4.1 Hz), 7.94 (q, 1H, J= 3.5 Hz), 7.42-7.38 (m, 2H), 7.30 (d, 2H, J= 7.6 Hz), 7.12 (t, 1H, J= 7.6 Hz), 6.89 (d, 1H, J= 8.2 Hz), 6.47 (dd, 1H, J= 2.3 and 8.8 Hz), 4.33 (s, 2H), 4.11-4.03 (m, 4H), 2.63 (d, 3H, J= 4.7 Hz), 2.08-2.03 (m, 2H). LCMS: ret. time: 17.33 min.; purity: 98%; MS (*m/e*): 440 (MH<sup>+</sup>).

**7.3.591 R935206: N2, N4-Bis[1-(N-methylaminocarbonyl)methyl-indazole-6-yl]-5-fluoro-2,4-pyrimidinediamine**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2, N4-Bis[1-(methoxycarbonyl)methyl-indazole-6-yl]-5-fluoro-2,4-pyrimidinediamine and was reacted with Me<sub>2</sub>NH.HCl and *i*-PrN<sub>2</sub>Et in presence of methanol to produce N2, N4-bis[1-(N-methylaminocarbonyl)methyl-indazole-6-yl]-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.56 (s, 1H), 9.40 (s, 1H), 8.17 (d, 1H, J= 3.5 Hz), 8.12 (s, 1H), 7.99 (s, 1H), 7.96 (s, 2H), 7.90 (s, 2H), 7.66 (d, 1H, J= 8.8 Hz), 7.56 (d, 1H, J= 8.8 Hz), 7.49 (dd, 1H, J= 1.7 and 8.8 Hz), 7.34 (dd, 1H, J= 1.7 and 8.8 Hz), 4.90 (s, 2H), 4.66 (s, 2H), 2.56 (d, 6H, J= 4.11 Hz). LCMS: ret. time: 13.85 min.; purity: 98%; MS (*m/e*): 503 (MH<sup>+</sup>).

**7.3.592 R935212: N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(N-methylaminocarbonyl)methyl-indazole-6-yl]-2,4-pyrimidinediamine**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazole-6-yl]-2,4-pyrimidinediamine and Me<sub>2</sub>NH.HCl was reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(N-methylaminocarbonyl)methyl-indazole-6-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.35 (s, 1H), 9.17 (s, 1H), 8.07 (d, 1H, J= 4.8 Hz), 7.92 (s, 1H),

7.89 (s, 1H), 7.66 (q, 1H, J= 4.7 Hz), 7.54 (d, 1H, J= 8.8 Hz), 7.35-7.24 (m, 3H), 6.76 (d, 1H, J= 8.8 Hz), 4.77 (s, 2H), 4.20 (s, 4H), 2.57 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 15.82 min.; purity: 94%; MS (*m/e*): 450 (MH<sup>+</sup>).

5                    **7.3.593    R935213: N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-(N-methylamino)carbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-methoxycarbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine was reacted with Me<sub>2</sub>NH.HCl and *i*-Pr<sub>2</sub>NEt. to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-(N-methylamino)carbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.17 (s, 2H), 8.30 (q, 1H, J= 4.7 Hz), 8.05 (d, 1H, J= 3.5 Hz), 7.42 (s, 1H), 7.29-7.19 (m, 2H), 7.09 (t, 1H, J= 8.2 Hz), 7.02 (d, 1H, J= 2.9 Hz), 6.76 (d, 1H, J= 8.8 Hz), 6.67 (d, 1H, J= 2.9 Hz), 6.54 (dd, 1H, J= 1.7 and 8.2 Hz), 4.94 (s, 2H), 4.21-4.18 (m, 4H), 2.70 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 18.85 min.; purity: 91%; MS (*m/e*): 492 (MH<sup>+</sup>).

20                    **7.3.594    R935216: 5-Fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine and Me<sub>2</sub>NH.HCl were reacted to provide 5-fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.31 (s, 1H), 9.00 (s, 1H), 8.17 (s, 1H), 8.02 (d, 1H, J= 3.5 Hz), 7.99 (m, 1H), 7.93 (s, 1H), 7.59 (m, 2H), 7.52 (d, 2H, J= 8.8 Hz), 6.78 (d, 2H, J= 8.8 Hz), 4.36 (s, 2H), 4.03 (s, 3H), 2.63 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 14.81 min.; purity: 99%; MS (*m/e*): 422 (MH<sup>+</sup>).

30                    **7.3.595    R935217: N2, N4-Bis[1-(N-methylaminocarbonyl)methyl-indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2, N4-bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine and

Me<sub>2</sub>NH.HCl were reacted to produce N2, N4-bis[1-(N-methylaminocarbonyl)methyl-indazole-5-yl]-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.35 (s, 1H), 9.15 (s, 1H), 8.09-8.06 (m, 2H), 7.97-7.96 (m, 2H), 7.91 (s, 1H), 7.70 (s, 1H), 7.69 (s, 1H), 7.64-7.55 (m, 2H), 7.48-7.40 (m, 2H), 5.06 (s, 2H), 4.97 (s, 2H), 2.62 (d, 3H, J= 4.7 Hz), 2.61 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 12.54 min.; purity: 95%; MS (*m/e*): 503 (MH<sup>+</sup>).

**7.3.596 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926486)**

A dry reaction vial equipped with a rubber septum was charged with N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (0.019 g, 0.04 mmol) and THF (1 mL). To this was added boranemethyl sulfide complex (0.044 mL, 0.088 mmol) and stirred at room temperature for 2h. The amount of boranemethyl sulfide complex was evaporated and the reaction was quenched with MeOH (CAUTION: vigorous evolution of hydrogen gas occurs during the addition of MeOH), heated for 30 min. The solvent was removed and again the residue was suspended in MeOH, extracted with EtOAc, EtOAc was evaporated and the residue was purified by preparative TLC to obtain N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.20 (s, 1H), 8.01 (d, 1H, J= 6 Hz), 7.26-7.05 (m, 3H), 7.05-6.97 (m, 3H), 6.82 (d, 1H, J= 9.3 Hz), 6.67 (dd, 1H, J= 1.8 and 8.1 Hz), 4.44 (t, 2H), 4.27 (s, 4H), 4.14 (m, 2H), 3.76 (m, 2H), 3.22 (t, 2H, J= 5.4 Hz), 3.05 (m, 2H), 2.88 (m, 2H).

**7.3.597 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine (R926490)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine with boranemethyl sulfide complex gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.65 (d, 2H, J= 2.1 Hz), 8.30 (dd, 2H, J= 2.1 and 9.6 Hz), 7.73 (d, 2H, J= 9.3 Hz), 7.49 (bs, 2H), 7.32 (m, 1H), 6.74 (m, 1H), 4.24 (s, 4H), 3.97 (s, 2H), 3.78 (m, 4H), 3.56 (m, 4H).

**7.3.598 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926510)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and boranemethyl sulfide complex gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.00 (d, 1H, J= 5.2 Hz), 7.50-7.30 (m, 2H), 7.16- 6.80 (m, 5H), 4.28 (m, 1H), 4.27 (bs, 4H), 4.22 (m, 1H), 3.44 (m, 2H), 2.79 (d, 3H, J= 3Hz); LCMS: ret. time: 15.64 min.; purity: 96%; MS (m/e): 412 (MH<sup>+</sup>).

**7.3.599 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine (R926770)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with boranemethyl sulfide complex gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.06 min.; purity: 75%; MS (m/e): 435 (MH<sup>+</sup>).

**7.3.600 N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R940255)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine with boranemethyl sulfide complex gave N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.94 min.; purity: 99 %; MS (m/e): 454 (MH<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.16 (1H, s), 9.07 (1H, s), 8.15 (1H, s), 8.11 (1H, d, J= 3.9 Hz), 7.40-7.30 (4H, m), 7.13 (1H, t, 8.1 Hz), 6.55 (1H, dd, J= 8.1 Hz, 3.2 Hz), 4.01 (2H, t, J= 5.7 Hz), 3.65 (4H, t, J= 4.2 Hz), 2.72 (2H, t, J= 5.7 Hz), 2.515 (4H, t, J= 4.5 Hz), 2.24 (6H, s).



**7.3.601 N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt (R945142)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was treated with boranemethyl sulfide complex to give N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethyloxy]phenyl]-2,4-pyrimidinediamine, which was then treated with 4N HCl in dioxane (3 mL) followed crystallization from MeOH/EtOAc to give N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 2.17 (s, 6H), 3.66 (m, 10H), 4.26 (t, J= 4.5 Hz, 2H), 6.93 (dd, J= 1.5, 7.2 Hz, 1H), 7.10-7.13 (m, 2H), 7.17 (s, 2H), 7.31 (t, J= 8.4 Hz, 1H), 7.98 (d, J= 6.0 Hz, 1H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): δ - 162.93; LCMS: ret. time: 13.25 min.; purity: 96.08%; MS (m/e): 453.09 (MH<sup>+</sup>).

**7.3.602 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-(2-hydroxyethyloxy)phenyl]-2,4-pyrimidinediamine (R945144)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of N2-(4-carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and boranemethyl sulfide complex gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>): δ 3.86 (t, J= 4.8 Hz, 2H), 4.04 (t, J= 4.8 Hz, 2H), 4.28 (m, 4H), 6.78 (d, J= 9.0 Hz, 1H), 6.86 (d, J= 9.0 Hz, 2H), 7.18 (dd, J= 2.7, 8.7 Hz, 1H), 7.47 (d, J= 2.7 Hz, 1H), 7.63 (d, J= 9.0 Hz, 2H), 7.91 (d, J= 3.6 Hz, 1H), 8.29 (br, 1H, NH), 8.31 (br, 1H, NH); <sup>19</sup>F NMR (282 MHz, acetone-*d*<sub>6</sub>): δ - 169.18; LCMS: ret. time: 17.41 min.; purity: 98.36%; MS (m/e): 399.01 (MH<sup>+</sup>).

**7.3.603 N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine Dihydrochloride Salt (R945150)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-

pyrimidinediamine was treated with boranemethyl sulfide complex to give N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethyloxy]phenyl]-2,4-pyrimidinediamine, which was then treated with 4N HCl in dioxane (3 mL) followed crystallization from MeOH/EtOAc to give N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 2.21 (s, 3H), 3.72 (m, 10H), 4.35 (t, J= 4.5 Hz, 2H), 6.95 (dt, J= 1.5 and 9.0 Hz, 1H), 7.11-7.14 (m, 2H), 7.26 (dd, J= 0.9 and 2.7 Hz, 1H), 7.34 (t, J= 8.4 Hz, 1H), 7.50 (d, J= 2.4 Hz, 1H), 8.03 (d, J= 5.4 Hz, 1H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): δ - 162.74; LCMS: ret. time: 14.50 min.; purity: 94.75%; MS (m/e): 472.98 (MH<sup>+</sup>).

**7.3.604 N4-(3,5-Dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine Dihydrochloride Salt (R945157)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was treated with boranemethyl sulfide complex to give N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethyloxy]phenyl]-2,4-pyrimidinediamine, which was then treated with 4N HCl in dioxane (3 mL) followed crystallization from MeOH/EtOAc to give N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 2.23 (s, 6H), 3.66 (m, 10H), 3.72 (s, 3H), 4.31 (t, J= 4.5 Hz, 2H), 6.95 (dd, J= 1.8 and 8.4 Hz, 1H), 7.09-7.15 (m, 2H), 7.27 (s, 2H), 7.32 (t, J= 8.1 Hz, 1H), 8.01 (d, J= 5.4 Hz, 1H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): δ - 162.71; LCMS: ret. time: 16.41 min.; purity: 97.50%; MS (m/e): 467.12 (MH<sup>+</sup>).

**7.3.605 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926501)**

The reaction of equivalent amount of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) in methanol at 0 °C followed by dilution with dry ethyl ether or ethyl acetate gave the precipitate. The resulting precipitate was isolated by filtration (and/or using centrifuse technique) to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-

piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.97 (d, 1H, J= 5.4 Hz), 7.92 (d, 1H, J= 1.8 Hz), 7.62 (d, 1H, J= 8.2 Hz), 7.48 (s, 1H), 7.43 (dd, 1H, J= J= 2.4 and 8.7 Hz), 7.17 (d, 1H, J=2.4 Hz), 6.98 (dd, 1H, J= 2.4 and 8.7 Hz), 6.77 (d, 1H, J= 8.7 Hz), 4.13 (m, 4H), 4.22 (s, 4H), 3.38 (t, 4H, J= 5.7 Hz);  
 5 LCMS: ret. time: 15.12 min; purity: 89%; MS (m/e): 491 (MH<sup>+</sup>).

**7.3.606 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926504)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt,  
 10 the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydrogen chloride gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.6  
 15 (bs, 1H), 9.04 (bs, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.25-7.00 (m, 5H), 7.81 (d, 1H, J= 8.7 Hz), 6.54 (d, 1H, J= 8.4 Hz), 4.74 (s, 2H), 4.22 (s, 4H), 3.64 (m, 4H), 3.11 (m, 4H); LCMS: ret. time: 15.34 min.; purity: 100%; MS (m/e): 481 (MH<sup>+</sup>).

**7.3.607 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-N-methylaminoethyl)phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926509)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt,  
 the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyloxy]phenyl]-2,4-pyrimidinediamine with hydrogen chloride (4M,  
 25 dioxane) gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 15.88 min.; purity: 92%; MS (m/e): 412 (MH<sup>+</sup>).

**7.3.608 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926511)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt,  
 the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-

morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine and hydrogen chloride gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.98 (d, 1H, J= 5.4 Hz), 7.34 (t, 1H, 8.4 Hz), 7.16-6.81 (m, 6H), 4.42 (m, 1H), 4.40 (m, 2H), 4.25 (m, 5H), 4.10 (m, 2H), 3.90 (bs, 2H), 3.60 (m, 4H); LCMS: ret. time: 16.39 min.; purity: 100%; MS (m/e): 468 (MH<sup>+</sup>).

**7.3.609 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926768)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with hydrogen chloride treatment gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.98 (bs, 1H), 9.05 (bs, 1H), 8.18 (d, 1H, J= 4.8 Hz), 8.01 (s, 1H), 7.58 (d, 1H, J= 8.7 Hz), 7.50 (bd, 1H), 7.35 (s, 1H), 7.24 (d, 1H, J= 2.4 Hz), 7.11 (dd, 1H, J= 3 and 9 Hz), 6.80 (d, 1H, J= 8.7 Hz), 4.22 (s, 4H), 4.20-3.60 (m, 8H), 3.20 (m, 2H); LCMS: ret. time: 14.91 min.; purity: 86%; MS (m/e): 505 (MH<sup>+</sup>).

**7.3.610 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt R926502)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine upon treatment with hydrogen chloride (4M, dioxane) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. <sup>1</sup>H NMR (CDCl<sub>3</sub>OD): δ 8.00 (s, 1H), 7.89 (s, 1H), 7.98 (s, 1H), 7.60 (d, 1H, J= 8.7 Hz), 7.45 (m, 3H), 7.16 (t, 1H, J= 8.1 Hz), 7.10 (m, 1H), 7.02 (dd, 1H, J= 1.2 and 7.2 Hz), 6.70 (dd, 1H, J= 2.4 and 8.4 Hz), 4.13 (m, 4H), 3.37 (t, 4H, J= 5.4 Hz), 3.38 (t, 4H, J= 5.7 Hz); LCMS: ret. time: 13.40 min; purity: 79%; MS (m/e): 450 (MH<sup>+</sup>).

**7.3.611 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine Dihydrochloride Salt (R926769)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine Dihydrochloride Salt. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.00 (d, 1H), 7.85 (bd, 1H), 7.75 (m, 3H), 7.60 (m, 2H), 7.40-7.15 (m, 4H), 7.05 (s, 1H), 7.00-6.800 (m, 3H), 4.65 (dd, 2H), 3.60 (m, 8H).

**7.3.612 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926773)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydrogen chloride (4M, dioxane) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.99 (d, 1H, J= 5.1 Hz), 7.29 (t, 1H, J= 8.1 Hz), 7.21-7.05 (m, 5H), 6.83 (dd, 1H, J= 2.4 and 8.7 Hz), 6.77 (bd, 1H), 4.79 (s, 2H), 3.83 (m, 2H), 3.78 (m, 2H), 3.25 (m, 2H); LCMS: ret. time: 12.27 min.; purity: 91%; MS (m/e): 439 (MH<sup>+</sup>).

**7.3.613 N2-[3-[2-(N, N-Dimethylamino)ethyloxy]phenyl]-N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926771)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the treatment of N4-(3,4-ethylenedioxyphenyl)-N2-[3-[2-(N, N-dimethylamino)ethyloxy]phenyl]-5-fluoro-2,4-pyrimidinediamine with equivalent amount of hydrogen chloride (4M, dioxane) gave N4-(3,4-ethylenedioxyphenyl)-N2-[3-[2-(N, N-dimethylamino)ethyloxy]phenyl]-5-fluoro-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 15.37 min.; purity: 93%; MS (m/e): 426 (MH<sup>+</sup>).

**7.3.614 N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R940256)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 15.78 min.; purity: 98 %; MS (M/e): 454 (MH<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.60 (1H, s), 9.58 (1H, s), 8.29 (1H, s), 8.20 (1H, s), 7.43 (1H, d, J= 9Hz), 7.38-7.30 (3H, m), 7.24 (1H, t, J= 9 Hz), 6.70 (1H, d, J= 9 Hz), 4.35 (2H, m), 4.05 (2H, m), 3.84 (4H, m), 3.65-3.50 (2H, m), 3.26 (2H, m), 2.25 (6H, s).

**7.3.615 N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R940269)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 14.74 min.; purity: 96 %; MS (m/e): 474 (M<sup>+</sup>), 475 (MH<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.03 (1H, s), 9.35 (2H, s), 9.06 (1H, s), 8.17 (1H, d, J= 3.9 Hz), 7.67 (1H, m), 7.52 (1H, m), 7.46 (1H, d, J= 8.7 Hz), 7.39 (1H, s), 7.24 (1H, t, J= 8.1 Hz), 6.66 (1H, d, J= 8.1 Hz), 4.33 (1H, m), 4.07 (1H, d, J= 13 Hz), 3.79 (1H, t, J= 12.5 Hz), 3.56 (4H, m), 3.49 (4H, m), 3.29 (1H, t, J= 12.5 Hz), 2.29 (3H, s).

**7.3.616 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926816)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the treatment of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine with equivalent

amount of hydrogen chloride (4M, dioxane) gave the N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride salt. LCMS: ret. time: 17.04 min., purity: 96%, MS (m/e): 426 (MH<sup>+</sup>).

5                    **7.3.617    N4-(3,4-Ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine (R926696)**

A dry reaction flask charged with N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine was reacted with diisobutylaluminum hydride (DIBALH) (5 equivalents) in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C (reaction was  
10 monitored by TLC) followed by treatment with Rochell's salt to yield N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.11 (s, 1H), 8.02 (d, 1H, J= 3.3 Hz), 7.96 (t, 1H, J= 1.8 Hz), 7.40-7.30 (m, 3H), 7.19 (dt, 1H, J= 3.6 and 8.1 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.59 (s, 1H), 4.52 (d, 2H, J= 5.1 Hz), 4.22 (s, 4H); <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): - 46802; LCMS: ret. time: 19.14 min.;  
15 purity: 95 %; MS (m/e): 409 (MH<sup>+</sup>).

**7.3.618    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(hydroxymethyl)-(1H)-indol-5-yl]-2,4-pyrimidinediamine (R926700)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-  
20 N2-[2-(methoxycarbonyl)-(1H)-indol-5-yl]-2,4-pyrimidinediamine was reduced with DIBALH to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(hydroxymethyl)-(1H)-indol-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.81 (d, 1H, J= 4.2 Hz), 7.23 (d, 1H, J= 1.8 Hz), 7.28-7.23 (m, 2H), 7.19 (t, 1H, J= 2.4 Hz), 7.12 (dd, 1H, J= 1.8 and 9.0 Hz), 7.07 (t, 1H, J= 8.4 Hz), 6.52 (ddd, 1H, J= 1.2 and 8.1 Hz), 6.30 (s, 1H), 4.71 (s, 2H); <sup>19</sup>F NMR  
25 (CD<sub>3</sub>OD): - 47971; LCMS: ret. time: 15.36 min.; purity: 100 %; MS (m/e): 366 (MH<sup>+</sup>).

**7.3.619    5-Fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-[4-(isopropoxy)phenyl]-2,4-pyrimidinediamine (R926705)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine was  
30 reduced with DIBALH to yield 5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.83 (d, 1H, J= 3.3 Hz),

7.81 (s, 1H), 7.50 (d, 2H, J= 9.0 Hz), 7.29 (d, 1H, J= 9.0 Hz), 7.22 (dd, 1H, J= 2.4 and 8.7 Hz), 6.84 (d, 2H, J= 8.7 Hz), 6.56 (d, 1H, J= 1.2 Hz), 4.64 (s, 2H), 4.56 (2q, 1H, J= 5.7 Hz), 1.31 (d, 6H, J= 6.0 Hz); <sup>19</sup>F NMR (CD<sub>3</sub>OD): - 47926; LCMS: ret. time: 21.03 min.; purity: 99 %; MS (m/e): 409 (MH<sup>+</sup>).

5                                **7.3.620    5-Fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926707)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine was reduced with  
10 DIBALH to yield 5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.37 (s, 1H), 9.17 (s, 1H), 9.12 (s, 1H), 8.06 (d, 1H, J= 3.9 Hz), 8.01 (d, 1H, J= 1.8 Hz), 7.41-7.35 (m, 2H), 7.26 (d, 1H, J= 8.1 Hz), 7.11-7.05 (m, 2H), 6.60 (s, 1H), 6.51 (dd, 1H, J= 2.4 and 8.4 Hz), 5.41 (t, 1H, J= 6.0 Hz), 4.51 (d, 2H, J= 5.7 Hz); LCMS: ret. time: 16.21 min.; purity: 95 %; MS (m/e): 367 (MH<sup>+</sup>).

15                                **7.3.621    N4-(4-*tert*-Butyl)phenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine (R926728)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced  
20 with DIBAL to yield N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.94 (d, 1H, J= 3.0 Hz), 7.54 (d, 2H, J= 9.0 Hz), 7.37 (d, 2H, J= 8.4 Hz), 7.29-7.35 (m, 1H), 7.19-7.14 (m, 2H), 7.06 (d, 1H, J= 8.1 Hz), 6.82 (d, 1H, J= 2.7 Hz), 6.57 (dd, 1H, J= 2.4 and 8.1 Hz), 4.04-4.00 (m, 2H), 3.93-  
25 3.89 (m, 2H), 1.33 (s, 9H); <sup>19</sup>F NMR (CDCl<sub>3</sub>): -47214; LCMS: ret. time: 22.39 min.; purity: 94 %; MS (m/e): 397 (MH<sup>+</sup>).

**7.3.622    5-(Hydroxymethyl)-N2-[3-(2-hydroxyethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926735)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(3-hydroxyphenyl)-5-methoxycarbonyl-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine  
30 was reduced with DIBALH to yield 5-(hydroxymethyl)-N2-[3-(2-



hydroxyethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.87 (s, 1H), 7.35 (t, 1H, J= 1.5 Hz), 7.15-7.08 (m, 5H), 6.57-6.50 (m, 2H), 4.56 (s, 2H), 3.92-3.86 (m, 2H), 3.84-3.79 (m, 2H); LCMS: ret. time: 14.11 min.; purity: 89 %; MS (m/e): 369 (MH<sup>+</sup>).

5                                    **7.3.623     5-Fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine R940289**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-isopropylphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine  
10 reacted with DIBALH to give 5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.03 min.; purity: 93 %; MS (m/e): 382 (M<sup>+</sup>), 384 (MH<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.36 (1H, s), 9.24 (1H, s), 8.20 (1H, d, J= 4.2 Hz), 7.85 (1H, d, J= 8.5 Hz), 7.57 (1H, s), 7.41 (1H, s), 7.33 (1H, t, J= 8.5 Hz), 7.17 (1H, t, J= 8.5 Hz), 7.05 (1H, d, J= 8.5 Hz), 6.56 (1H, dd, J= 8.5 Hz, J= 2 Hz), 4.94 (1H, t, J= 12 Hz), 3.94 (2H, t, J= 4.7 Hz), 3.76 (2H, m), 2.95 (1H, sept, J= 6.9 Hz), 1.28 (6H, dd, J= 6.9 Hz, J= 0.6 Hz).  
15

**7.3.624     N4-(3-*tert*-Butylphenyl)-5-fluoro-N2-[(2-hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine R940287**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine reacted with  
20 DIBALH to give N4-(3-*tert*-butylphenyl)-5-fluoro-N2-[2-(hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine. LCMS: retn, time: 23.15 min.; purity: 99 %; MS (m/e): 407 (MH<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.34 (1H, s), 9.22 (1H, s), 8.18 (1H, d, J= 3.9 Hz), 8.04 (1H, s), 8.00 (1H, d, J= 8.7 Hz), 7.60 (1H, t, J= 2.1 Hz), 7.47 (2H, m), 7.34 (1H, t, J= 7.8 Hz), 7.21 (1H, d, J= 8.7 Hz), 6.69 (1H, s), 5.54 (1H, t, J= 5.8 Hz), 4.63 (2H, d, J= 5.8 Hz), 1.35 (9H, s).  
25

30                                    **7.3.625     5-Fluoro-N4-(3-isopropylphenyl)-N2-[(2-hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine R940286**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-

isopropylphenyl)-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine reacted with DIBALH to give 5-fluoro-N4-(3-isopropylphenyl)-N2-[(2-hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 21.93 min.; purity: 99 %; MS (m/e): 393 (M<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.33 (1H, s), 9.23 (1H, s), 8.18 (1H, d, J= 3.9 Hz), 8.03 (1H, s), 7.86 (1H, d, J= 7.1 Hz), 7.57 (1H, s), 7.49 (2H, m), 7.33 (1H, t, J= 7.1 Hz), 7.05 (1H, d, J= 7.1 Hz), 6.69 (1H, s), 5.54 (1H, t, J= 5.7 Hz), 4.63 (2H, d, J= 5.7 Hz), 2.90 (1H, sept, J= 6.9 Hz), 1.26 (6H, d, J= 6.9 Hz).

**7.3.626 N4-(3-*tert*-Butylphenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine R940282**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine reacted with DIBALH to give N4-(3-*tert*-butylphenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine.

LCMS: ret. time: 21.63 min.; Purity: 98 %; MS (m/e): 396 (M<sup>+</sup>).

**7.3.627 N4-[3,4-Bis(hydroxymethyl)phenyl]-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940292)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-[6-(3,3-dihydroisobenzofuranyl-1-one)]-5-fluoro-2,4-pyrimidinediamine reacted with DIBALH to give N4-[3,4-bis(hydroxymethyl)phenyl]-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.06 min.; purity: 100 %; MS (m/e): 400 (M<sup>+</sup>).

**7.3.628 (R935149): N2-(3,4-Ethylenedioxyphenyl)-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-5-fluoro-2,4-pyrimidinediamine**

2-Chloro-5-fluoro-N4-[4-[ethoxycarbonyl(dimethyl)methyl]phenyl]-N2-(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine was reduced with 10 eq. DIBALH (1.0 M in toluene) at 0 °C in dichloromethane. Reaction was quenched with methanol, diluted with ethylacetate followed by the addition of aqueous Rochelle's salt solution, stirred at room temperature for 30 minutes followed by the addition of anhydrous sodium sulfate. The solution was filtered through Celite, concentrated and purified the concentrated by silica gel

column chromatography to furnish the N2-(3,4-ethylenedioxyphenyl)-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.01 (br s, 1H), 9.6 (br s, 1H), 8.13 (d, 1H, J= 4.7 Hz), 7.58 (d, 2H, J= 8.2 Hz), 7.31 (d, 2H, J= 8.8 Hz), 7.18 (d, 1H, J= 2.3 Hz), 6.88 (dd, 1H, J= 2.3 and 8.8 Hz), 6.73 (d, 1H, J= 8.8 Hz),  
 5 4.21-4.19 (m, 4H), 3.56 (br s, 2H), 1.20 (s, 6H); LCMS: ret. time: 20.34 min.; purity: 98%; MS (*m/e*): 411 (MH<sup>+</sup>).

**7.3.629 (R935151): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine**

10 In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.89 (d, 1H, J= 2.9  
 15 Hz), 7.46 (d, 3H, J= 8.8 Hz), 7.27 (d, 2H, J= 8.2 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.68-6.65 (m, 1H), 4.53 (septet, 1H, J= 5.8 Hz), 3.57 (s, 2H), 1.36 (d, 6H, J= 5.8 Hz), 1.31 (s, 6H); LCMS: ret. time: 23.43 min.; purity: 99%; MS (*m/e*): 411 (MH<sup>+</sup>).

**7.3.630 (R935153): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine:**

20 In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[4-[ethoxycarbonyl(dimethyl)methyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ  
 25 7.89 (d, 1H, J= 2.9 Hz), 7.57 (s, 1H), 7.41 (d, 2H, J= 8.8 Hz), 7.29 (d, 2H, J= 8.2 Hz), 7.16 (d, 1H, J= 8.2 Hz), 7.10 (d, 1H, J= 8.8 Hz), 6.80-6.55 (m, 2H), 5.58 (s, 2H), 1.30 (s, 6H); LCMS: ret. time: 18.01 min.; purity: 98%; MS (*m/e*): 369 (MH<sup>+</sup>).

**7.3.631 (R935154): N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine**

30 In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyoxyphenyl)-2,4-

pyrimidinediamine was reduced with DIBALH to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.88 (d, 1H, J= 3.8 Hz), 7.34 (t, 1H, J= 2.3 Hz), 7.19 (dd, 1H, J= 2.3 and 8.2 Hz), 7.14 (d, 1H, J= 7.6 Hz), 7.01-6.97 (m, 2H), 6.84 (d, 1H, J= 8.8 Hz), 6.53 (dd, 1H, J= 1.7 and 7.6 Hz), 4.26 (s, 4H), 3.98 (t, 2H, J= 4.1 Hz), 3.89 (t, 2H, J= 4.1 Hz); LCMS: ret. time: 18.36 min.; purity: 99%; MS (*m/e*): 399 (MH<sup>+</sup>).

**7.3.632 (R935155): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine:**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine was reduced to 5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine with DIBALH. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.73 (d, 1H, J= 3.5 Hz), 7.33 (d, 2H, J= 8.8 Hz), 7.15 (br s, 1H), 7.04 (app t, 2H, J= 8.2 and 7.6 Hz), 6.78 (d, 2H, J= 8.8 Hz), 6.49 (d, 1H, J= 7.6 Hz), 3.95 (t, 2H, J= 4.7 Hz), 3.80 (t, 2H, J= 4.7 Hz); LCMS: ret. time: 14.49 min.; purity: 98%; MS (*m/e*): 357 (MH<sup>+</sup>).

**7.3.633 (R935156): 5-Fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.90 (d, 1H, J= 3.5 Hz), 7.45 (d, 2H, J= 8.8 Hz), 7.34 (t, 1H, J= 2.3 Hz), 7.13 (t, 1H, J= 8.2 Hz), 6.93 (m, 3H), 7.76 (d, 1H, J= 2.3 Hz), 6.52 (dd, 1H, J= 2.3 and 8.2 Hz), 4.52 (septet, 1H, J= 5.7 Hz), 3.95-3.85 (m, 4H), 1.34 (d, 6H, J= 5.7 Hz); LCMS: ret. time: 21.17 min.; purity: 98%; MS (*m/e*): 399 (MH<sup>+</sup>).

**7.3.634 (R935158): 5-Fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[4-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine:**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[4-[1-ethoxycarbonyl]-

5 methyl)ethyl]phenyl]-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[4-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.83 (d, 1H, J= 3.5 Hz), 7.49 (d, 2H, J= 8.8 Hz), 7.35 (d, 2H, J= 8.8 Hz), 7.31 (d, 2H, J= 8.8 Hz), 6.82 (d, 2H, J= 8.8 Hz), 4.03 (t, 2H, J= 4.7 Hz), 3.89 (t, 2H, J= 4.7 Hz), 3.56 (s, 2H), 1.30 (s, 6H); LCMS: ret. time: 16.86 min.; purity: 96%; MS (*m/e*): 413 (MH<sup>+</sup>).

**7.3.635 (R935160): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine:**

10 In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.12 (s, 1H), 8.92 (s, 1H), 7.98 (d, 1H, J= 3.5 Hz), 7.59 (d, 2H, J= 8.8 Hz), 7.49 (d, 2H, J= 9.3 Hz), 6.86 (d, 2H, J= 8.8 Hz), 6.76 (d, 2H, J= 9.3 Hz), 4.82 (t, 1H, J= 4.9 Hz), 4.55 (septet, 1H, J= 6.4 Hz), 3.89 (t, 2H, J= 5.3 Hz), 3.67 (app q, 2H, J= 5.3 and 4.9 Hz), 1.24 (d, 6H, J= 6.4 Hz); LCMS: ret. time: 19.56 min.; purity: 100%; MS (*m/e*): 399 (MH<sup>+</sup>).

20 **7.3.636 (R935161): 5-Fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine**

25 In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-N2-(3-methoxycarbonylmethylphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.27 (s, 1H), 9.11 (s, 1H), 8.07 (d, 1H, J= 3.5 Hz), 7.67 (d, 2H, J= 8.8 Hz), 7.38-7.24 (m, 4H), 7.06 (t, 1H, J= 8.2 Hz), 6.46 (dd, 1H, J= 8.2 Hz), 4.83 (t, 1H, J= 5.3 Hz), 4.66 (t, 1H, J= 5.3 Hz), 3.88 (t, 2H, J= 5.3 Hz), 3.67 (t, 1H, J= 5.3 Hz), 3.66 (t, 1H, J= 5.3 Hz), 3.38 (d, 2H, J= 5.3 Hz), 1.20 (s, 6H); LCMS: ret. time: 17.17 min.; purity: 96%; MS (*m/e*): 413 (MH<sup>+</sup>).

**7.3.637 (R935168): 5-Fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to produce 5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.21 (s, 1H), 8.93 (s, 1H), 8.00 (d, 1H, J = 4.1 Hz), 7.62 (d, 2H, J = 8.8 Hz), 7.48 (d, 2H, J = 8.8 Hz), 7.27 (d, 2H, J = 8.8 Hz), 6.75 (d, 2H, J = 8.8 Hz), 4.65 (t, 1H, J = 5.3 Hz), 4.47 (septet, 1H, J = 5.8 Hz), 3.38 (d, 2H, J = 5.3 Hz), 1.22 (d, 6H, J = 5.8 Hz), 1.20 (s, 6H); LCMS: ret. time: 22.97 min.; purity: 99%; MS (*m/e*): 411 (MH<sup>+</sup>).

**7.3.638 (R935170): 5-Fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine:**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-hydroxyphenyl)-N4-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to produce 5-fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.23 (s, 1H), 9.14 (s, 1H), 9.06 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 7.51 (dd, 1H, J = 1.7 and 7.6 Hz), 7.30 (app t, 1H, J = 2.3 and 1.7 Hz), 7.19 (t, 1H, J = 8.2 Hz), 7.13 (br s, 1H), 7.11 (m, 1H), 6.96 (t, 1H, J = 7.6 Hz), 6.61 (dd, 1H, J = 2.3 and 8.2 Hz), 6.28 (dd, 1H, J = 2.3 Hz and 8.2 Hz), 4.84 (t, 1H, J = 5.8 Hz), 3.92 (t, 2H, J = 5.2 Hz), 3.68 (app qt, 2H, J = 5.2 Hz); LCMS: ret. time: 14.71 min.; purity: 96%; MS (*m/e*): 357 (MH<sup>+</sup>).

**7.3.639 (R935171): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-pyrimidine-2,4-diamine, N4-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.24 (s, 1H), 9.13 (s, 1H), 9.01 (s, 1H), 8.04 (d, 1H, J = 3.5 Hz), 7.68 (d, 2H, J = 8.8 Hz), 7.29 (d, 2H, J = 8.8 Hz),

7.16 (br s, 1H), 7.07 (m, 1H), 6.94 (t, 1H, 8.8 Hz), 6.30 (m, 1H), 4.64 (t, 1H, J= 5.8 Hz), 3.38 (d, 2H, J= 5.3 Hz), 1.20 (s, 6H); LCMS: ret. time: 17.36 min.; purity: 100%; MS (*m/e*): 369 (MH<sup>+</sup>).

5                    **7.3.640    (R935174): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-(2-carbomethoxybenzofur-5-yl)-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2[4-(2-hydroxyethoxy)phenyl]-N2-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.26 (s, 1H), 8.94 (s, 1H), 8.01 (d, 1H, J= 4.1 H), 7.99 (s, 1H), 7.52-7.45 (m, 4H), 6.72 (d, 2H, J= 9.3 Hz), 6.66 (s, 1H), 5.46 (t, 1H, J= 5.3 Hz), 4.82 (t, 1H, J= 5.8 Hz), 4.55 (d, 2H, J= 5.8 Hz), 3.89 (t, 2H, J= 5.3 Hz), 3.67 (app qt, 2H, J= 5.3 Hz); LCMS: ret. time: 14.97 min.; purity: 91%; MS (*m/e*): 411 (MH<sup>+</sup>).

15                    **7.3.641    (R935176): N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine:**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.22 (s, 1H), 8.98 (s, 1H), 8.05 (d, 1H, J= 3.5 Hz), 7.47 (dd, 1H, J= 1.1 and 8.2 Hz), 7.27 (t, 1H, J= 1.7 Hz), 7.23 (d, 1H, J= 2.3 Hz), 7.18 (t, 1H, J= 8.2 Hz), 7.05 (dd, 1H, J= 2.3 and 8.8 Hz), 6.68 (d, 1H, J= 8.2 Hz), 6.61 (dd, 1H, J= 1.7 and 8.8 Hz), 4.85 (t, 1H, J= 5.3 Hz), 4.18-4.14 (m, 4H), 3.91 (t, 2H, J= 5.3 Hz), 3.68 (qt, 2H, J= 5.3 Hz); LCMS: ret. time: 17.35 min.; purity: 92%; MS (*m/e*): 399 (MH<sup>+</sup>).

30                    **7.3.642    (R935177): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(2-carbomethoxybenzofur-5-yl)-N2-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-2,4-

pyrimidinediamine was reduced with DIBALH to produce 5-fluoro- N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 18.17 min.; purity: 94%; MS (*m/e*): 423 (MH<sup>+</sup>).

5                    **7.3.643    (R935178): 5-Fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(2-carbomethoxybenzofur-5-yl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.93 (s, 1H), 9.12 (s, 1H), 8.07 (d, 1H, J= 3.6 Hz), 8.01 (d, 1H, J= 2.3 Hz), 7.55-7.46 (m, 2H), 7.29 (br s, 1H), 7.23 (d, 1H, J= 8.2 Hz), 7.03 (t, 1H, J= 8.2 Hz), 6.68 (s, 1H), 6.44 (dd, 1H, J= 2.3 and 8.2 Hz), 5.47 (t, 1H, J= 5.8 Hz), 4.80 (t, 1H, J= 5.3 Hz), 4.55 (d, 2H, J= 5.3 Hz), 3.81 (qt, 2H, J= 5.3 Hz), 3.63 (qt, 2H, J= 5.3 Hz); LCMS: ret. time: 15.41 min.; purity: 88%; MS (*m/e*): 411 (MH<sup>+</sup>).

**7.3.644    (R935181): N4-(3,5-Dimethoxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3,5-dimethoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidineamine was reduced with DIBALH to give N4-(3,5-dimethoxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.24 (s, 1H), 9.18 (s, 1H), 8.11 (d, 1H, J= 3.5 Hz), 7.31-7.26 (m, 2H), 7.05 (d, 1H, J= 8.2 Hz), 6.99 (d, 1H, J= 2.3 Hz), 6.43 (dd, 1H, J= 2.3 Hz, 8.2 Hz), 6.20 (t, 1H, J= 2.3 Hz), 4.80 (t, 1H, J= 5.8 Hz), 3.83 (t, 2H, J= 5.3 Hz), 3.67 (s, 6H), 3.66-3.60 (m, 2H); LCMS: ret. time: 18.78 min.; purity: 95%; MS (*m/e*): 400 (MH<sup>+</sup>).

**7.3.645    (R935183): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reduced with DIBAL-H to provide 5-fluoro-N2-[4-(2-



hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.15 (s, 1H), 8.97 (s, 1H), 8.00 (d, 1H, J = 3.5 Hz), 7.49 (d, 2H, J = 8.8 Hz), 7.40-7.31 (m 2H), 6.88 (d, 1H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 4.82 (t, 1H, J = 5.3 Hz), 4.12-4.04 (m 4H), 3.90 (t, 2H, J = 5.2 Hz), 3.70-3.65 (app qt, 2H, J = 5.3 Hz), 2.07 (q, 2H, J = 5.3 Hz); LCMS: ret. time: 17.05 min.; purity: 96%; MS (*m/e*): 413 (MH<sup>+</sup>).

**7.3.646 (R935186): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.21 (s, 1H), 9.14 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.42-7.36 (m, 2H), 7.29-7.24 (m, 2H), 7.07 (t, 1H, J = 8.2 Hz), 6.90 (d, 1H, J = 8.8 Hz), 6.45 (dd, 1H, J = 1.7 and 8.3 Hz), 4.82 (t, 1H, J = 5.3 Hz), 4.12-4.04 (app q, 2H, J = 5.3 Hz), 3.86 (t, 2H, J = 5.3 Hz), 3.67 (app qt, 2H, J = 5.3 Hz), 2.07 (q, 2H, J = 5.3 Hz); LCMS: ret. time: 17.95 min.; purity: 96%; MS (*m/e*): 413 (MH<sup>+</sup>).

**7.3.647 N4-(4-*tert*-Butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine (R926720)**

The reaction of N2-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine and lithium hydroxide (LiOH) in THF:H<sub>2</sub>O at room temperature gave N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.01 (bs, 1H), 9.69 (bs, 1H), 8.13 (d, 1H, J = 4.8 Hz), 7.57 (d, 2H, J = 8.7 Hz), 7.50 (s, 1H), 7.35 (d, 2H, J = 8.1 Hz), 7.13 (d, 1H, J = 8.7 Hz), 6.75 (d, 1H, J = 9.0 Hz), 5.21 (dd, 1H, J = 6.3 and 10.5 Hz), 3.49 (dd, 1H, J = 10.5 and 16.5 Hz), 3.17 (dd, 1H, J = 6.6 and 16.5 Hz), 1.27 (s, 9H); LCMS: ret. time: 22.53 min.; purity: 93 %; MS (*m/e*): 423 (MH<sup>+</sup>).

**7.3.648 N4-(4-*tert*-Butylphenyl)-N2-(3-carboxymethyleneoxyphenyl)-5-fluor-2,4-pyrimidinediamine (R926726)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and lithium

hydroxide were reacted to yield N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(3-carboxymethyleneoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.88 (bs, 1H), 9.29 (s, 1H), 9.16 (s, 1H), 8.07 (d, 1H, J= 3.3 Hz), 7.68 (d, 2H, J= 8.7 Hz), 7.35-7.31 (m, 3H), 7.26 (d, 1H, J= 8.4 Hz), 7.06 (t, 1H, J= 8.4 Hz), 6.41 (dd, 1H, J= 2.4 and 8.4 Hz),  
 5 4.54 (s, 2H), 1.27 (s, 9H); <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): - 46463; LCMS: ret. time: 22.94 min.; purity: 97 %; MS (m/e): 411 (MH<sup>+</sup>).

**7.3.649 5-Fluoro-N2-[3-(carboxymethyleneoxy)phenyl]- N4-[4-(isopropoxy)phenyl]-2,4-pyrimidinediamine (R926731)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine and lithium hydroxide were reacted to yield 5-fluoro-N2-(3-carboxymethyleneoxyphenyl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 6.19 (bs, 1H), 9.01 (s, 1H), 8.02 (d, 1H, J= 3.9 Hz), 7.63 (d, 2H, J= 9.3 Hz), 7.19-7.14 (m, 2H), 6.96 (t, 1H, J= 8.7 Hz), 6.87 (d, 2H, J= 9.6 Hz), 6.28 (dd, 1H, J= 2.45 and 9.0 Hz), 4.56 (2q, 1H, J= 6.6 Hz), 3.94 (s, 2H), 1.24 (d, 6H, J= 6.6 Hz); LCMS: ret. time: 20.13 min.; purity: 100 %; MS (m/e): 413 (MH<sup>+</sup>).

**7.3.650 N2,N4-Bis(4-carboxymethyleneoxy)phenyl-5-fluoro-2,4-pyrimidinediamine (R926560)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, the hydrolysis of N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with LiOH gave N2,N4-bis(4-carboxymethyleneoxy)phenyl-5-fluoro-2,4-pyrimidinediamine <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.86 (bs, 1H), 7.55 (d, 2H, J= 9.0 Hz), 7.32 (bd, 2H, J= 9.3 Hz), 6.95 (m, 4H),  
 25 4.66 (s, 2H), <sup>19</sup>F NMR (CDCl<sub>3</sub>): - 21852; LCMS: ret. time: 15.16 min.; purity: 77%; MS (m/e): 429 (MH<sup>+</sup>).

**7.3.651 N2-(3-Carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926483)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-

pyrimidinediamine with LiOH gave N2-(3-carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.90 (s, 1H), 9.20 (s, 2H), 8.05 (d, 1H, J= 1.2 Hz), 7.32-7.21 (m, 3H), 7.08 (t, 1H, J= 8.1 Hz), 6.80 (d, 1H, J= 8.4 Hz), 6.40 (dd, 1H, J= 1.8 and 8.2 Hz), 4.53 (s, 2H), 4.20 (s, 4H); LCMS: ret. time: 18.26 min.; purity: 100%; MS (m/e): 413 (MH<sup>+</sup>).

**7.3.652 N2-(3-Carboxymethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945126)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with LiOH gave N2-(3-carboxymethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 4.55 (s, 2H), 6.43 (dd, J= 2.1, 8.1 Hz, 1H), 6.48 (dd, J= 2.1 and 7.2 Hz, 1H), 7.06-7.13 (m, 3H), 7.28-7.34 (m, 3H), 8.09 (d, J= 3.6 Hz, 1H), 9.22 (br, 1H), 9.28 (br, 1H), 9.34 (br, 1H); <sup>19</sup>F NMR (282 MHz, DMSO-d<sub>6</sub>): δ -163.85; LCMS: ret. time: 15.88 min.; purity: 100%; MS (m/e): 370.63 (MH<sup>+</sup>).

**7.3.653 N2-(4-Carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926238)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine with LiOH gave N2-(carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.16 (d, 1H, J= 4.8 Hz), 7.37 (bd, 2H, J= 9 Hz), 7.25 (d, 1H, J= 3Hz), 7.08 (m, 1H), 6.83 (m, 3H), 4.64 (s, 2H), 4.23 (s, 4H); LCMS: ret. time: 19.15 min.; purity: 100%; MS (m/e): 413 (MH<sup>+</sup>).

**7.3.654 N2-(4-Carboxymethyleneoxyphenyl)-5-Fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926564)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine upon treatment with LiOH gave 5-fluoro-N2-(4-carboxymethyleneoxyphenyl)-N4-(3-

hydroxyphenyl)-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.89 (d, 1H,  $J = 5.1$  Hz), 7.34 (dd, 2H,  $J = 2.1$  and 9.3 Hz), 7.19-7.08 (m, 2H), 6.98 (dd, 2H,  $J = 2.4$  and 8.4 Hz), 6.69 (m, 1H), 4.68 (s, 2H);  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{OD}$ ): - 21860; LCMS: ret. time: 15.69 min.; purity: 99%; MS (m/e): 371 ( $\text{MH}^+$ ).

5                                **7.3.655    N2-(2-Carboxybenzofuran-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926478)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-4-pyrimidinediamine upon LiOH  
10 treatment gave N2-(2-carboxybenzofuran-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.97 (bd, 2H), 7.60-7.44 (m, 4H), 7.20-7.05 (m, 3H), 6.69 (bd, 1H);  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{OD}$ ): - 21844; LCMS: ret. time: 16.77 min.; purity: 100%; MS (m/e): 381 ( $\text{MH}^+$ ).

15                                **7.3.656    N2-(2-Carboxyindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926479)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, N2-(2-ethoxycarbonylindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine upon LiOH treatment gave  
20 N2-(2-carboxyindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.83 (m, 1H), 7.73 (s, 1H), 7.50 (bd, 1H,  $J = 8.7$  Hz), 7.30-7.11 (m, 5H), 6.68 (bd, 1H); LCMS: ret. time: 16.50 min.; purity: 97%; MS (m/e): 380 ( $\text{MH}^+$ ).

**7.3.657    N4-(4-*tert*-Butylphenyl)-N2-(2-carboxybenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R926481)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, LiOH treatment with N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine  
25 gave N4-(4-*tert*-butylphenyl)-N2-(2-carboxybenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  9.3 (bd, 2H), 8.25 (s, 1H), 8.10 (s, 1H), 7.65-7.30 (m, 5H), 1.25 (s, 9H);  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{OD}$ ): - 21844; LCMS: ret. time: 23.32 min.;  
30 purity: 100%; MS (m/e): 421 ( $\text{MH}^+$ ).

**7.3.658 N4-(3-*tert*-Butylphenyl)-N2-[3-carboxymethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine R940280**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reacted with LiOH to give N4-(3-*tert*-butylphenyl)-N2-(3-carboxymethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 23.61 min.; purity: 99 %; MS (m/e): 410 (M<sup>+</sup>), 412 (MH<sup>+</sup>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.45 (1H, s), 9.33 (1H, s), 8.21 (1H, d, J= 3.9 Hz), 7.98 (1H, d, J= 6.6 Hz), 7.60 (1H, t, J= 2 Hz), 7.44-7.34 (3H, m), 7.24-7.15 (2H, m), 6.54 (1H, d, J= 7.8 Hz), 4.68 (2H, s), 1.36 (9H, s).

**7.3.659 N2-(3-Carboxymethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950190)**

The reaction of N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (0.1 g) and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave the solid. The resulting solid was filtered, washed with water and dried to give N2-(3-carboxymethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 18.23 min.; purity: 87.6%; MS (m/e): 412.01 (MH<sup>+</sup>).

**7.3.660 N2-(Carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethyloxy)phenyl]-2,4-pyrimidinediamine (R950230)**

In a manner similar to the preparation of N2-(3-carboxymethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the hydrolysis of N2-(ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylenoxy)phenyl]-2,4-pyrimidinediamine with LiOH gave N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethyloxy)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.15 min.; purity: 78.3%; MS (m/e): 413.01 (MH<sup>+</sup>).

**7.3.661 5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950231)**

A mixture of N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (10 mg), 2-aminoethanol (10 equiv.) and PyBroP (2 equiv.) was stirred in 0.5 ml DMF for 24 hours at room temperature. The

mixture was diluted with water, extracted with EtOAc and the organic phase was dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel (CHCl<sub>3</sub>:Acetone, 2:1) to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethylene aminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.98 min.; purity: 92.6%; MS (m/e): 455.97 (MH<sup>+</sup>).

**7.3.662 N2-[3-(N-2-Aminoethylamino)carbonylmethylene aminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylenoxy)phenyl]-2,4-pyrimidinediamine (R950232)**

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and 1,2-ethylenediamine were reacted to afford N2-[3-(N-2-aminoethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylenoxy)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 11.31 min.; purity: 93.6%; MS (m/e): 454.94 (MH<sup>+</sup>).

**7.3.663 5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950233)**

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and methylamine were reacted to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.93 min.; purity: 92.9%; MS (m/e): 426.27 (MH<sup>+</sup>).

**7.3.664 5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-methylamino)ethylamino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950234)**

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N-methylethylenediamine were reacted to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-methylamino)ethylamino]

carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 11.39 min.; purity: 97.7%; MS (m/e): 468.96 (MH<sup>+</sup>).

5                    **7.3.665    N2-[3-[N-(2-N-Benzylamino)ethylamino]carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (R950235)**

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N-benzylethylenediamine were reacted to give N2-[3-[N-(2-N-benzylamino)ethylamino]carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.39 min.; purity: 97.3%; MS (m/e): 545.01 (MH<sup>+</sup>).

15                    **7.3.666    5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950236)**

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and morpholine were reacted to afford 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.24 min.; purity: 94.6xx%; MS (m/e): 482.40 (MH<sup>+</sup>).

25                    **7.3.667    N2-[3-(3-N,N-Dimethylaminopropyl)aminocarbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (R950237)**

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N,N-dimethylpropanediamine were reacted to give N2-[3-(3-N,N-Dimethylaminopropyl)aminocarbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.33 min.; purity: 91.4%; MS (m/e): 497.47 (MH<sup>+</sup>).

**7.3.668 N2-[3-[N-(2,3-Dihydroxypropyl)amino]carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (R950238)**

5 In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and 1-amino-2,3-propanediol were reacted to give N2-[3-[N-(2,3-dihydroxypropyl)amino]carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.86 min.; purity: 90.0%; MS (m/e): 486.40 (MH<sup>+</sup>).

**7.3.669 5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950239)**

15 In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and 4-(2-aminoethyl)morpholine were reacted to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.52 min.; purity: 92.4%; MS (m/e): 525.47 (MH<sup>+</sup>).

**7.3.670 2,4-Bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine (R926514)**

and

**25 5-Ethoxycarbonyl-2-methoxy-4-[N-(L)-tyrosine methyl ester]pyrimidine (R926513)**

A mixture of tyrosine methyl ester (58 mg, 0.3 mmol), 2,4-dichloro-5-ethoxycarbonylpyrimidine (44 mg, 0.1 mmol) in MeOH (2mL) was heated in a sealed tube at 100 °C for a period of overnight, diluted with H<sub>2</sub>O (20 mL), acidified with 2N HCl and extracted with ethyl acetate (3 x 25 mL). The solvent was evaporated and the residue was purified by preparative TLC using 30% EtOAc/Hexanes to obtain a mixture of 2,4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine (R926514). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ



8.60 (1H, J= 6.6 Hz), 8.36 (s, 1H), 7.05 (d, 2H, J= 8.7 Hz), 6.84 (d, 2H, J= 8.1 Hz), 6.74 (d, 2H, J= 9 Hz), 6.54 (d, 2H, J= 9 Hz), 4.82 (t, 2H, J= 6 Hz), 4.25 (q, 2H, J= 6.3 Hz), 3.73 (s, 3H), 3.72 (s, 3H), 3.06 (m, 4H), 1.31 (t, 3H, J= 7.2 Hz) and 5-ethoxycarbonyl-2-methoxy-4-[N-(L)-tyrosine methyl ester]pyrimidine (**R926513**): <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.78 (s, 1H), 8.65 (d, 1H, J= 6.9 Hz), 7.02 (dd, 2H, J= 2.1 and 6.3 Hz), 6.77 (dd, 2H, J= 2.4 and 6.6 Hz), 4.93 (q, 1H, J= 1.5 and 6.9 Hz), 4.30 (q, 2H, J= 8.1 Hz), 3.90 (s, 3H), 3.70 (s, 3H), 3.17 (dd, 1H, J= 5.4 Hz), 3.06 (dd, 1H, J= 7.5 and 7.8 Hz), 1.33 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 22.58 min.; purity: 99%; MS (m/e): 376 (M<sup>+</sup>).

10 **7.3.671 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926252)**

In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with 3,4-ethylenedioxyaniline gave N2,N4-bis(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.01 (s, 1H), 9.65 (bs, 1H), 8.62 (s, 1H), 7.18 (bs, 2H), 7.04 (dd, 1H, J= 1.8 and 8.7 Hz), 6.93 (d, 1H, J= 7.5 Hz), 6.76 (d, 1H, J= 8.7 Hz), 6.65 (d, 1H, J= 8.7 Hz), 4.28 (q, 2H, J= 6.9 Hz), 1.31 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 27.25 min.; purity: 100%; MS (m/e): 451 (MH<sup>+</sup>).

20 **7.3.672 N2,N4-Bis(4-methoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926253)**

In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with ethyl 4-aminophenoxyacetate gave N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (**R926253**). <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.60 (bs, 1H), 7.4 (bs, 1H), 7.33 (d, 4H, J= 9Hz), 6.94 (bd, 4H), 4.76 (s, 2H), 4.75 (s, 2H), 4.44 (q, 2H, J= 6.9 Hz), 3.79 (s, 3H), 1.40 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 25.83 min.; purity: 89%; MS (m/e): 511 (MH<sup>+</sup>).

25 **7.3.673 2,4-Bis[N-(L)-phenylalaninyl ethyl ester]-5-ethoxycarbonylpyrimidine (R926526)**

In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with ethyl (L)-phenylalanine ethyl ester in MeOH or EtOAc gave 2,4-bis[N-(L)-phenylalanine ethyl ester]-5-ethoxycarbonylpyrimidine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.55 (d, 1H, J= 7.2 Hz), 8.51

(s, 1H), 7.35-7.10 (m, 10H), 5.88 (d, 1H, J= 6 Hz), 4.88 (ddd, 1H, J= 6.3 Hz), 4.80 (ddd, 1H, J= 6.3 Hz), 4.23 (q, 2H, J= 7.2 Hz), 4.12 (q, 4H, J= 7.2 Hz), 3.65 (t, 2H, J= 6 Hz), 3.56 (t, 2H, J= 6.0 Hz), 1.30 (t, 2H, J= 6 Hz), 1.30 (t, 3H, J= 7.2 Hz), 1.20 (m, 6H); LCMS: ret. time: 32.22 min.; purity: 89%; MS (m/e): 535 (MH<sup>+</sup>).

5                                    **7.3.674    2,4-Bis[N-(L)-valinyl ethyl ester]-5-ethoxycarbonylpyrimidine (R926527)**

In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with ethyl (L)-valine ethyl ester in MeOH or EtOAc gave 2,4-bis[N-(L)-valinyl ethyl ester]-5-ethoxycarbonylpyrimidine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.59 (d, 1H, J= 7.8 Hz), 8.56 (s, 1H), 5.69 (d, 1H, J= 8.7 Hz), 4.62 (m, 1H), 4.51 (m, 1H), 4.25 (q, 2H, J= 7.5 Hz), 4.20 (m, 4H), 2.20 (m, 2H), 1.34 (t, 3H, J= 7.8 Hz), 1.27 (t, 6H, J= 7.5 Hz), 1.00 (m, 12H); LCMS: ret. time: 29.27 min.; purity: 97%; MS (m/e): 439 (MH<sup>+</sup>).

15                                    **7.3.675    5-Ethoxycarbonyl-N2-(3-hydroxyphenyl)-4-[N-(L)-phenylalanine ethyl ester]-2-pyrimidineamine (R926528)**

The reaction of 2-chloro-N4-(3-hydroxyphenyl)-5-ethoxycarbonylpyrimidineamine with 3 equivalents of (L)-N-phenylalanine ethyl ester in methanol at 80-100 °C for 24 h followed by dilution with water and acidification with 2N HCl have the acidic solution. The resulting solution was extracted with EtOAc and the residue was purified by silics gel column chromatography to afford 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.4 (bs, 1H), 9.13 (d, 1H, J= 6 Hz), 8.45 (bs, 1H), 7.59 (s, 1H), 7.34-7.25 (m, 5H), 7.15 (t, 1H, J= 8.1 Hz), 6.73 (bd, 1H, J= 7.5 Hz), 6.67 (dd, 1H, J= 1.8 and 7.8 Hz), 4.86 (dt, 1H, J= 3 and 5.1 Hz), 4.32 (q, 2H, J= 6.3 Hz), 4.19 (q, 2H, J= 7.2 Hz), 3.30 (dd, 1H, J= 4.8 and 8.7 Hz), 3.18 (dd, 1H, J= 5.1 and 8.7 Hz), 1.36 (t, 3H, J= 6.9 Hz), 1.65 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 27.49 min.; purity: 91%; MS (m/e): 451 (MH<sup>+</sup>).

**7.3.676    N2-(3,4-Ethylenedioxyphenyl)-5-ethoxycarbonyl-4-[N-(L)-phenyl glyciny ethyl ester]-2-pyrimidineamine (R926536)**

In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of 2-chloro-5-ethoxycarbonyl-4-[N-(L)-phenyl glyciny ethyl ester]pyrimidine with 3,4-ethylenedioxyaniline in MeOH or EtOAc gave N2-(3,4-ethylenedioxyphenyl)-5-

ethoxycarbonyl-4-[N-(L)-phenyl glyciny ethyl ester]-2-pyrimidineamine.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  9.15 (s, 1H), 8.9 (s, 1H), 8.61 (s, 1H), 7.48 (m, 2H), 7.38 (m, 3H), 7.16 (bs, 1H), 6.80 (m, 2H), 5.75 (d, 1H), 4.24 (m, 6H), 3.66 (s, 3H), 1.35 (t, 3H); LCMS: ret. time: 28.16 min.; purity: 85%; MS (m/e): 465 ( $\text{MH}^+$ ).

5                                **7.3.677    N4-(4-tert-Butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926579)**

10                                In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-ethoxycarbonyl-4-pyrimidineamine with methyl 4-aminophenoxyacetate gave N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  10.17 (s, 1H), 8.73 (s, 1H), 8.45 (bs, 1H), 7.49 (d, 2H,  $J=8.7$  Hz), 7.43 (d, 2H,  $J=8.7$  Hz), 7.33 (bs, 1H), 6.87 (d, 2H,  $J=6$  Hz), 6.84 (d, 2H,  $J=5.7$  Hz), 4.63 (s, 2H), 4.53 (s, 2H), 4.33 (q, 2H,  $J=6.9$  Hz), 3.81 (s, 3H), 1.49 (s, 9H), 1.39 (t, 3H,  $J=7.5$  Hz); LCMS: ret. time: 27.93 min.; purity: 96%; MS (m/e): 553 ( $\text{MH}^+$ ).

20                                **7.3.678    N4-(4-tert-Butoxycarbonylmethyleneoxyphenyl)-N2-(4-methoxycarbonylmethyleneoxyphenyl)-5-methoxycarbonyl-2,4-pyrimidinediamine (R926580)**

25                                In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-ethoxycarbonyl-4-pyrimidineamine with methyl 4-aminophenoxyacetate gave N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-methoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. 5-methyl ester was obtained due to the cross esterification reaction in MeOH.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  10.13 (s, 1H), 8.73 (s, 1H), 8.45 (bs, 1H), 7.49 (d, 2H,  $J=8.7$  Hz), 7.43 (d, 2H,  $J=8.7$  Hz), 7.33 (bs, 1H), 6.87 (m, 4H), 4.63 (s, 2H), 4.53 (s, 2H), 4.33 (q, 2H,  $J=6.9$  Hz), 3.88 (s, 3H), 3.81 (s, 3H), 1.49 (s, 9H); LCMS: ret. time: 27.43 min.; purity: 100%; MS (m/e): 539 ( $\text{MH}^+$ ).

30

**7.3.679 N4-(4-Carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926583)**

The treatment of N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with trifluoroacetic acid in THF:H<sub>2</sub>O at room temperature afforded N4-(4-carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.03 (s, 1H), 8.65 (s, 1H), 7.49 (bd, 4H, J= 8.7 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.81 (d, 2H, J= 8.1 Hz), 4.70 (s, 2H), 4.65 (s, 2H), 4.33 (q, 2H, J= 6.9 Hz), 3.81 (s, 3H), 1.49 (s, 9H), 1.39 (t, 3H, J= 7.5 Hz); LCMS: ret. time: 22.28 min.; purity: 73%; MS (m/e): 497 (MH<sup>+</sup>).

**7.3.680 N2-(4-Carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926584)**

The treatment of N2-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with trifluoroacetic acid in THF:H<sub>2</sub>O at room temperature afforded N2-(4-carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.01 (s, 1H), 8.64 (s, 1H), 7.45 (bd, 4H, J= 7.2 Hz), 6.90 (d, 2H, J= 8.7 Hz), 6.75 (d, 2H, J= 8.4 Hz), 4.80 (s, 2H), 4.38 (s, 2H), 4.26 (q, 2H, J= 7.2 Hz), 3.70 (s, 3H), 1.30 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 22.37 min.; purity: 100%; MS (m/e): 497 (MH<sup>+</sup>).

**7.3.681 5-Carboxy-N2-(3-hydroxyphenyl)-N4-[N-(L)-phenylglycine]-2-pyrimidineamine (R926535)**

The LiOH hydrolysis of N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-4-[N-(L)-phenylglycine ethyl ester]-2-pyrimidineamine afforded 5-carboxy-N2-(3-hydroxyphenyl)-N4-[N-(L)-phenylglycine]-2-pyrimidineamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.89 (s, 1H), 8.50 (s, 1H), 7.43 (m, 2H), 7.33 (m, 3H), 7.14 (m, 2H), 6.98 (m, 2H), 6.62 (m, 1H), 5.71 (s, 1H); LCMS: ret. time: 17.75 min.; purity: 73%; MS (m/e): 382 (MH<sup>+</sup>).

**7.3.682 5-Amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925856)**

A suspension of 6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-5-nitro-2,4-pyrimidinediamine and 10% Pd/C (10% by weight) in ethanol was prepared and reacted in

a Parr bottle under hydrogen gas (20 PSI) for 1h. The reaction mixture was filtered through Celite. Purification by column chromatography gave 5-amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.30 (bs, 1H), 7.18-7.10 (m, 3H), 7.00 (t, 2H, J= 8.1 Hz), 6.59-6.54 (m, 1H), 6.33 (dd, 1H, J= 2.1 and 11.1 Hz), 4.39 (q, 2H, J= 6.9 Hz), 1.43 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 19.24 min.; purity: 100 %; MS (m/e): 382 (MH<sup>+</sup>).

**7.3.683 5-Amino-6-ethoxycarbonyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine (R925857)**

In a manner similar to the preparation of 5-amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine, 6-ethoxycarbonyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-5-nitro-2,4-pyrimidinediamine, hydrogen, and 10% Pd/C were reacted to yield 5-amino-6-ethoxycarbonyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.16 (d, 1H, J= 2.4 Hz), 7.07 (d, 1H, J= 2.4 Hz), 7.04 (dd, 1H, J= 2.4 and 9.0 Hz), 6.84-6.79 (m, 2H), 6.70 (d, 1H, J= 9.0), 4.43 (q, 2H, J= 7.8 Hz), 4.25 (s, 4H), 4.21 (bs, 4H), 1.43 (t, 3H, J= 7.8 Hz); LCMS: ret. time: 23.70 min.; purity: 100 %; MS (m/e): 466 (MH<sup>+</sup>).

**7.3.684 5-Amino-N2,N4-bis(ethoxycarbonylmethyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine (R925865)**

In a manner similar to the preparation of 5-amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine, 6-ethoxycarbonyl-N2,N4-bis(ethoxycarbonylmethyl)-5-nitro-2,4-pyrimidinediamine, hydrogen, and 10% Pd/C were reacted to yield 5-amino-N2,N4-bis(ethoxycarbonylmethyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 6.25 (bs, 2H), 4.38 (q, 2H, J= 6.9 Hz), 4.23-4.14 (m, 6H), 4.05 (bs, 2H), 1.39 (t, 3H, J= 6.9 Hz), 1.30-1.22 (m, 6H); LCMS: ret. time: 17.67 min.; purity: 95 %; MS (m/e): 370 (MH<sup>+</sup>).

**7.3.685 5-Amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine (R926567)**

Hydrogenation of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine using Pd/C in MeOH at 40 PSI gave 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.47 (d, 2H, J= 8.7 Hz), 7.41 (d, 2H, J= 8.7 Hz), 6.88 (d, 2H, J= 8.1 Hz), 6.81 (d, 2H, J= 8.7 Hz), 4.63 (s, 2H), 4.59 (s, 2H), 4.41 (q, 2H, J=

7.5 Hz), 4.29 (m, 4H), 1.44 (t, 3H), 1.31 (m, 6H); LCMS: ret. time: 26.15 min.; purity: 97%; MS (m/e): 554 (MH<sup>+</sup>).

5                    **7.3.686    N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine (R926571)**

A dry reaction flask equipped with a rubber septum and a N<sub>2</sub> inlet was charged with 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine, equimolar amount of pyridine and phenyl isocyanate at room temperature. The reaction was allowed to stirred at room temperature for overnight and the  
10    resulting reaction was poured over n-hexane to precipitate the desired product, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.92 (s, 1H), 7.47 (s, 1H), 7.35 (bt, 5H, J= 8.4 Hz), 7.25 (bt, 2H, J= 7.5 Hz), 7.03 (m, 2H), 6.81 (d, 2H, J= 8.7 Hz), 6.76 (d, 2H, J= 8.7 Hz), 4.60 (s, 2H), 4.58 (s, 2H), 4.29 (m, 6H), 1.45 (m, 9H); LCMS: ret. time: 27.75 min.; purity:  
15    91%; MS (m/e): 673 (MH<sup>+</sup>).

**7.3.687    5-Allylaminocarbonylamino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine (R926585)**

In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the  
20    reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with allyl isocyanate gave 5-allylaminocarbonylamino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine. LCMS: ret. time: 25.60 min.; purity: 91%; MS (m/e): 637 (MH<sup>+</sup>).

25                    **7.3.688    N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(ethoxycarbonylamino)-2,4-pyrimidinetriamine (R926586)**

In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the  
30    reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with ethoxycarbonyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-

(ethoxycarbonylaminocarbonylamino)-2,4-pyrimidinediamine. LCMS: ret. time: 26.79 min.; purity: 88%; MS (m/e): 669 (MH<sup>+</sup>).

5                    **7.3.689    N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(ethoxycarbonylmethyleneaminocarbonylamino)-2,4-pyrimidinediamine (R926587)**

In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with ethylacetyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-  
10 (ethoxycarbonylmethyleneaminocarbonylamino)-2,4-pyrimidinediamine. LCMS: ret. time: 25.76 min.; purity: 96%; MS (m/e): 683 (MH<sup>+</sup>).

15                    **7.3.690    N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(cyclopentylaminocarbonylamino)-2,4-pyrimidinediamine (R926588)**

In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with cyclopentyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-  
20 (cyclopentylaminoacrbonylamino)-2,4-pyrimidinediamine . LCMS: ret. time: 27.36 min.; purity: 83%; MS (m/e): 665 (MH<sup>+</sup>).

25                    **7.3.691    N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(chloroacetylaminocarbonylamino)-2,4-pyrimidinediamine (R926589)**

In like manner to the preparation of N2,N4-bis(ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(N-phenylformyl-amino)-2,4-pyrimidinediamine, the reaction of N5-amino-N2,N4-bis(ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with chloroacetylformyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(chloroacetylamino  
30 carbonylamino)-2,4-pyrimidinediamine. LCMS: ret. time: 26.60 min.; purity: 100%; MS (m/e): 580 (MH<sup>+</sup>).

**7.3.692 (R920669): N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-trifluoro-2,4-pyridinediamine**

A mixture of 2,4-dichloro-5-trifluoromethylpyrimidine (416 mg, 1.9 mmol), 3,4-ethylenedioxyaniline (0.5 mL, 4.1 mmol), and concentrated HCl (0.1 mL) in 1:9 acetone/H<sub>2</sub>O (10 mL) was heated to reflux. After 1 h, the reaction was complete as determined by TLC. The mixture was cooled to room temperature and EtOAc (30 mL) was added. The organic layer was washed with 2 N HCl (2 x 15 mL), water (15 mL), and dried (Na<sub>2</sub>SO<sub>4</sub>). The organic layer was filtered through a silica gel pad, washing the filter cake with EtOAc, and concentrated. The material was purified by chromatography (silica gel, 95:5 dichloromethane/ethyl acetate) to afford N2,N4-bis(3,4-ethylenedioxyphenyl)-5-trifluoro-2,4-pyridinediamine (380 mg, 44%): *R<sub>f</sub>* 0.27 (silica gel, 9.5:0.5 dichloromethane/ethyl acetate); mp 141-143 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.25 (s, 1H), 7.07 (m, 2H), 6.99 (bs, 1H), 6.93-6.84 (m, 3H), 6.77-6.74 (m, 1H), 6.67 (bs, 1H), 4.29-4.24 (m, 8H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 161.2, 157.9, 155.8, 143.7, 132.6, 131.1, 117.5, 117.3, 114.4, 113.2, 110.3, 64.7, 64.5; IR (ATR) 3446 cm<sup>-1</sup>; ESI MS *m/z* 447 [C<sub>21</sub>H<sub>17</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub> + H]<sup>+</sup>; HPLC (Method C) >99% (AUC), *t<sub>R</sub>* = 8.5 min. Anal. Calcd for C<sub>21</sub>H<sub>17</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>: C, 56.50; H, 3.84; N, 12.55. Found: C, 56.46; H, 4.41; N, 12.57.

**7.3.693 (R920668): N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-pyridyl)-2,4-pyrimidinediamine**

A mixture of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (280 mg, 1 mmol), 3-aminopyridine (113 mg, 1.2 mmol), sodium *t*-butoxide (134 mg, 1.4 mmol), binap (38 mg, 0.06 mmol), and palladium(II)acetate (14 mg, 0.06 mmol) in 9 mL of toluene was purged with N<sub>2</sub> (3 cycles of alternating N<sub>2</sub> and vacuum). The mixture was heated to 80 °C (oil-bath temperature). After 24 h, the mixture was cooled to room temperature and EtOAc (30 mL) and of water (10 mL) was added. After stirring 15 min, the precipitate was collected by filtration. A <sup>1</sup>H NMR spectrum and ESI mass spectrum of the solid (150 mg) indicated the product (TLC analysis of the organic layer of the filtrate detected only starting materials). The crude product was slurried in 2 N HCl and the mixture was filtered. The filtrate was neutralized with 10% aqueous NaOH and concentrated. The material was slurried with MeOH and the solids removed by filtration. The concentrated material was slurried in CH<sub>3</sub>CN and TFA was added to afford a solution. *N,N*-diisopropylethylamine was added to the solution and the solid was collected by filtration, washing with CH<sub>3</sub>CN followed by Et<sub>2</sub>O to afford N4-(3,4-ethylenedioxyphenyl)-



5-fluoro-N2-(3-pyridyl)-2,4-pyrimidinediamine (55 mg, 14%):  $R_f$  0.42 (silica gel, 4:1:0.1:0.1 dichloromethane/ethyl acetate/methanol/concentrated ammonium hydroxide); mp 251-253 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.38 (s, 1H), 9.26 (s, 1H), 8.74 (s, 1H), 8.20-8.17 (m, 1H), 8.09-8.08 (m, 2H), 7.29-7.28 (m, 1H), 7.23-7.17 (m, 2H), 6.83-6.80 (m, 1H), 4.24 (m, 4H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  155.2, 149.8, 142.9, 141.6, 140.5, 140.0, 139.8, 139.7, 137.5, 132.1, 124.8, 123.0, 116.4, 115.1, 110.9, 64.1, 64.0; IR (ATR) 3264, 3195  $\text{cm}^{-1}$ ; APCI MS  $m/z$  340 [ $\text{C}_{17}\text{H}_{14}\text{FN}_5\text{O}_2 + \text{H}$ ] $^+$ . Anal. Calcd for  $\text{C}_{17}\text{H}_{14}\text{FN}_5\text{O}_2 \cdot 0.5\text{H}_2\text{O}$ : C, 58.70; H, 4.20; N, 20.13. Found: C, 58.71; H, 4.20; N, 19.51.

7.3.694 (R920664): N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-n-hexyloxyphenyl)-2,4-pyrimidindiamine

To a magnetically stirred solution of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (0.25 g, 0.89 mmol) in ethylene glycol (3.0 mL) under nitrogen at room temperature was added *N,N*-diisopropylethylamine (0.12 g, 0.89 mmol) followed by 4-hexyloxyaniline (0.27 g, 1.4 mmol). The reaction mixture was heated to 170 °C for 5.5 h, cooled to room temperature and partitioned between water (20 mL) and chloroform (20 mL). The aqueous layer was extracted with chloroform (20 mL) and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The crude brown solid was purified by chromatography (silica gel, 2:1 hexanes/ethyl acetate) to afford N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-n-hexyloxyphenyl)-2,4-pyrimidindiamine (0.09 g, 23%) as a white solid:  $R_f$  0.53 (silica gel, 4:1 chloroform/ethyl acetate); mp 115-117 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 (d,  $J$  = 3.2 Hz, 1H), 7.40 (d,  $J$  = 8.9 Hz, 2H), 7.29 (d,  $J$  = 2.5 Hz, 2H), 6.98 (d,  $J$  = 8.8 Hz, 1H), 6.88-6.82 (m, 3H), 6.61 (s, 1H), 4.29 (d,  $J$  = 3.1 Hz, 4H), 3.94 (t,  $J$  = 6.6, 6.7 Hz, 2H), 1.77 (m, 2H), 1.47 (m, 2H), 1.35 (m, 4H), 0.92 (m, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.3, 155.1, 150.3, 143.6, 142.7, 140.3, 140.0, 139.4, 133.0, 131.7, 121.9, 117.3, 115.0, 114.7, 110.8, 68.6, 64.6, 31.8, 29.5, 25.9, 22.8, 14.2; IR (ATR) 3357  $\text{cm}^{-1}$ ; ESI MS  $m/z$  439 [ $\text{C}_{24}\text{H}_{27}\text{FN}_4\text{O}_3 + \text{H}$ ] $^+$ ; HPLC (Method B) 98.5% (AUC),  $t_R$  = 7.9 min. Anal. Calcd for  $\text{C}_{24}\text{H}_{27}\text{FN}_4\text{O}_3$ : C, 65.74; H, 6.21; N, 12.78. Found: C, 65.34; H, 6.19; N, 12.96.

7.3.695 (R920666): N2-(4-n-Butyloxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine

To a magnetically stirred solution of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (0.25 g, 0.89 mmol) in ethylene glycol (3.0 mL) under nitrogen at

room temperature was added *N,N*-diisopropylethylamine (0.12 g, 0.89 mmol) followed by 4-butoxyaniline (0.18 g, 1.1 mmol). The reaction mixture was heated to 185 °C for 5 h, cooled to room temperature, and partitioned between water (20 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL) and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The crude brown solid was purified by chromatography (silica gel, 2:1 hexanes/ethyl acetate) to afford N2-(4-n-Butyloxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine (0.18 g, 49%) as a tan solid: *R*<sub>f</sub> 0.66 (silica gel, 4:1 chloroform/ethyl acetate); mp 133-135 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.89 (d, *J* = 3.2 Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 2H), 7.28 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 8.7, 2.5 Hz, 1H) 6.90-6.81 (m, 4H), 6.60 (d, *J* = 2.4 Hz, 1H), 4.27 (s, 4H), 3.94 (t, *J* = 6.5 Hz, 2H), 1.80-1.71 (m, 2H), 1.55-1.42 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 156.3, 155.1, 150.4, 143.6, 142.7, 140.3, 140.0, 139.4, 133.0, 131.7, 121.9, 117.3, 115.0, 114.7, 110.8, 68.2, 64.7, 64.5, 31.6, 19.4, 14.0; IR (ATR) 3356 cm<sup>-1</sup>; ESI MS *m/z* 411 [C<sub>22</sub>H<sub>23</sub>FN<sub>4</sub>O<sub>3</sub> + H]<sup>+</sup>; HPLC (Method A) >99% (AUC), *t*<sub>R</sub> = 17.3 min. Anal. Calcd for C<sub>22</sub>H<sub>23</sub>FN<sub>4</sub>O<sub>3</sub>: C, 64.38; H, 5.65; N, 13.65. Found: C, 62.64; H, 5.59; N, 13.15.

**7.3.696 (R920670): N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine**

To a solution of 2-chloro-N4-(4-ethyloxyphenyl)-5-fluoro-4-pyrimidineamine (0.25 g, 0.93 mmol) in ethylene glycol (3 mL) under nitrogen at room temperature was added *i*-Pr<sub>2</sub>EtN, 0.93 mmol) followed by 3,4-ethylenedioxyaniline (0.17 g, 1.12 mmol). The reaction mixture was heated to 200 °C for 5 h and then cooled to room temperature. The mixture was partitioned between H<sub>2</sub>O (20 mL) and EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated in vacuo. The crude brown solid was purified by chromatography (2:1 CHCl<sub>3</sub>/EtOAc) to afford N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (0.21 g, 60%) as a tan solid: *R*<sub>f</sub> 0.42 (4:1 CHCl<sub>3</sub>/EtOAc); mp 163.8-167.2 °C (DSC); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.89 (d, *J* = 2.8 Hz, 1H), 7.50-7.45 (m, 2H), 7.17 (d, *J* = 2.5 Hz, 1H), 6.92-6.86 (m, 3H), 6.80-6.75 (m, 2H), 6.64 (bs, 1H), 4.26-4.21 (m, 4H), 4.03 (q, *J* = 7.0, 2H), 1.42 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 156.1, 150.6, 143.6, 142.8, 140.3, 140.0, 139.5, 139.3, 134.0, 130.8, 123.2, 117.2, 115.1, 113.6, 109.4, 64.6, 64.0, 15.1; IR (ATR) 3403 cm<sup>-1</sup>; ESI MS *m/z* 383 [C<sub>20</sub>H<sub>19</sub>FN<sub>4</sub>O<sub>3</sub>

+ H]<sup>+</sup>; HPLC (Method A) 98.1% (AUC), *t*<sub>R</sub> = 12.0 min. Anal. Calcd for C<sub>20</sub>H<sub>19</sub>FN<sub>4</sub>O<sub>3</sub>: C, 62.82; H, 5.01; N, 14.65. Found: C, 62.06; H, 5.01; N, 14.35.

**7.3.697 (R920671): N4-(4-n-Butyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine**

5 In like manner to the preparation of N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(4-n-butyloxyphenyl)-5-fluoro-4-pyrimidineamine with 3,4-ethylenedioxyaniline gave N4-(4-n-butyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine. The crude product was purified by chromatography (2:1 CHCl<sub>3</sub>/EtOAc) ; (0.17 g, 52%) as a tan solid:  
 10 *R*<sub>f</sub> 0.51 (4:1 CHCl<sub>3</sub>/EtOAc); mp 149.6-151.4 °C (DSC); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.88 (d, *J* = 3.4 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.91-6.86 (m, 3H), 6.78-6.75 (m, 2H), 6.62 (bs, 1H), 4.26-4.22 (m, 4H), 3.96 (t, *J* = 6.5, 2H), 1.82-1.73 (m, 2H), 1.56-1.44 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 156.1, 150.8, 143.6, 142.8, 140.2, 139.9, 139.5, 139.2, 133.9, 130.7, 123.1, 117.1, 115.0, 113.5, 109.4,  
 15 68.2, 64.6, 31.6, 19.4, 14.0; IR (ATR) 3365 cm<sup>-1</sup>; ESI MS *m/z* 411 [C<sub>22</sub>H<sub>23</sub>FN<sub>4</sub>O<sub>3</sub> + H]<sup>+</sup>; HPLC (Method A) 99.0% (AUC), *t*<sub>R</sub> = 13.2 min. Anal. Calcd for C<sub>22</sub>H<sub>23</sub>FN<sub>4</sub>O<sub>3</sub>: C, 64.38; H, 5.65; N, 13.65. Found: C, 63.63; H, 5.60; N, 13.38.

**7.3.698 (R920672): N4-(4-n-Hexyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine**

20 In like manner to the preparation of N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(4-n-hexyloxyphenyl)-5-fluoro-4-pyrimidineamine with 3,4-ethylenedioxyaniline gave N4-(4-n-hexyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine. The crude product was purified by chromatography (2:1 CHCl<sub>3</sub>/EtOAc) (0.22 g, 69%) as a tan solid: *R*<sub>f</sub>  
 25 0.54 (4:1 CHCl<sub>3</sub>/EtOAc); mp 124.0-125.2 °C (DSC); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.88 (d, *J* = 3.2 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.91-6.86 (m, 3H), 6.78-6.74 (m, 2H), 6.62 (d, *J* = 1.8 Hz, 1H), 4.26-4.22 (m, 4H), 3.96 (t, *J* = 6.5, 2H), 1.83-1.74 (m, 2H), 1.51-1.42 (m, 2H), 1.36-1.32 (m, 4H), 0.93-0.89 (t, *J* = 6.7 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 156.1, 150.5, 143.5, 143.0, 142.8, 140.2, 139.9, 139.5, 139.2, 133.9,  
 30 130.7, 123.1, 117.1, 115.0, 113.5, 109.3, 68.5, 64.7, 64.5, 31.8, 29.5, 25.9, 22.8, 14.2; IR (ATR) 3378 cm<sup>-1</sup>; ESI MS *m/z* 439 [C<sub>24</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>3</sub> + H]<sup>+</sup>; HPLC (Method A) >99% (AUC),

$t_R = 14.6$  min. Anal. Calcd for  $C_{24}H_{27}FN_4O_3$ : C, 65.74; H, 6.21; N, 12.78. Found: C, 65.52; H, 6.23; N, 12.66.

**7.3.699 (R920818): 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine**

5 To a mixture of 4-amino-[(1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (1.2 g, 6.2 mmol), 1-propanol (40 mL) and trifluoroacetic acid (1 mL) was added 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyridineamine (1.5 g, 6.2 mmol). The mixture was heated at 110 °C for 17 h and then cooled to room temperature. The purple solid that formed was collected by filtration, washing with 1-propanol (30 mL) to afford 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (1.6 g, 65%) as an off-white solid:  $R_f$  0.55 (6:3:1  $CHCl_3/CH_3OH/NH_4OH$ ); mp (DSC) 191.2-193.7 °C, 257.2-260.0 °C, 344.7-345.2 °C;  $^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  9.39 (s, 1H), 9.21 (s, 1H), 9.10 (s, 1H), 8.04 (d,  $J = 3.8$  Hz, 1H), 7.59 (d,  $J = 9.1$  Hz, 2H), 7.38 (s, 1H), 7.23 (t,  $J = 8.1$  Hz, 1H), 7.17 (d,  $J = 1.8$  Hz, 1H), 7.05 (t,  $J = 8.1$  Hz, 1H), 6.93 (d,  $J = 9.1$  Hz, 2H), 6.50 (dd,  $J = 1.8, 8.1$  Hz, 1H), 5.40 (s, 2H);  $^{13}C$  NMR (75 MHz,  $DMSO-d_6$ )  $\delta$  157.3, 155.3, 153.5, 151.9, 149.8, 149.7, 141.0 (d,  $J_{C-F} = 150.0$  Hz), 139.7, 138.7, 135.0, 128.9, 120.2, 114.8, 110.3, 108.7, 59.6; IR (ATR) 3338, 2923, 2581, 1724, 1661, 1580, 1557  $cm^{-1}$ ; ESI MS  $m/z$  395 [ $C_{18}H_{15}FN_8O_2 + H$ ] $^+$ ; HPLC (Method A) 96.5% (AUC),  $t_R = 6.9$  min.

**7.3.700 (R920819): N4-(3-Hydroxyphenyl)-N2-[4-(1H,1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine**

20 To a mixture of 4-amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene (0.1 g, 0.5 mmol), 1-propanol (2 mL) and trifluoroacetic acid (0.2 mL) was added 2-chloro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (0.1 g, 0.5 mmol). The mixture was heated at 110 °C for 17 h and then cooled to room temperature. The purple solid that formed was collected by filtration, washing with 1-propanol (5 mL) to afford N4-(3-hydroxyphenyl)-N2-[4-(1H,1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (59.4 mg, 30%) as an off-white solid:  $R_f$  0.51 (6:3:1  $CHCl_3/CH_3OH/NH_4OH$ ); mp 292-295 °C dec;  $^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  9.34 (s, 2H), 9.13 (s, 1H), 7.95 (d,  $J = 5.8$  Hz, 1H), 7.64 (d,  $J = 8.9$  Hz, 2H), 7.39 (s, 1H), 7.19 (t,  $J = 8.1$  Hz, 1H), 7.05 (t,  $J = 8.1$  Hz, 1H), 6.96 (d,  $J = 8.9$  Hz, 2H), 6.43 (dd,  $J = 1.4, 8.1$  Hz, 1H), 6.20 (d,  $J = 5.8$  Hz, 1H), 5.40 (s, 2H);  $^{13}C$  NMR (75 MHz,  $DMSO-d_6$ )  $\delta$  160.4, 158.5, 157.5, 154.0, 153.7, 152.2, 140.6, 134.4, 129.1, 120.9,

114.7, 111.0, 109.5, 107.2, 98.4, 59.6; IR (ATR) 3321, 2920, 2581, 1649, 1605, 1487  $\text{cm}^{-1}$ ; ESI MS  $m/z$  377 [ $\text{C}_{18}\text{H}_{16}\text{N}_8\text{O}_2 + \text{H}$ ] $^+$ ; HPLC (Method A) 97.6% (AUC),  $t_R = 7.6$  min.

**7.3.701 (R920820): N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(1H,1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine**

To a mixture of 4-amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene (0.2 g, 0.9 mmol), 1-propanol (4 mL) and trifluoroacetic acid (0.2 mL) was added 2-chloro-N4-(3-hydroxyphenyl)-5-methyl-4-pyrimidineamine (0.2 g, 0.9 mmol). The mixture was heated at 110 °C for 17 h and then cooled to room temperature. The purple solid that formed was collected by filtration, washing with 1-propanol (10 mL) to afford N4-(3-hydroxyphenyl)-5-methyl-N2-[4-(1H,1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (0.3 g, 89%) as an off-white solid:  $R_f$  0.44 (6:3:1  $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ ); mp (DSC) 255.3-262.4 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.32 (s, 1H), 9.65 (s, 2H), 7.85 (s, 1H), 7.38 (d,  $J = 10.5$  Hz, 2H), 7.17 (s, 1H), 7.12 (t,  $J = 7.9$  Hz, 1H), 7.06 (s, 1H), 6.90 (d,  $J = 10.5$  Hz, 2H), 6.68 (d,  $J = 7.9$  Hz, 1H), 5.45 (s, 2H), 2.14 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  161.6, 157.9, 154.5, 153.7, 151.2, 140.4, 138.2, 130.1, 129.4, 123.3, 115.9, 115.4, 113.5, 112.4, 107.5, 59.8, 13.7; IR (ATR) 3214, 3051, 2157, 1632, 1596, 1547  $\text{cm}^{-1}$ ; ESI MS  $m/z$  391 [ $\text{C}_{19}\text{H}_{18}\text{N}_8\text{O}_2 + \text{H}$ ] $^+$ ; HPLC (Method A) >99% (AUC),  $t_R = 7.9$  min.

**7.3.702 N4-(3-Benzyloxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine [NEED R NO.]**

A mixture of N4-(3-benzyloxyphenyl)-2-chloro-4-pyrimidineamine (0.25 g, 0.82 mmol), 4-amino-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.17 g, 0.82 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (10 mL) was heated to 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol, the crude product was preadsorbed onto silica gel using 95:5 methylene chloride /methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give N4-(3-benzyloxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a tan solid (0.20 g, 52%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.00 (br s, 1H), 7.86 (d,  $J = 6.1$  Hz, 1H), 7.53-7.20 (m, 13H), 7.14 (d,  $J = 9.0$  Hz, 2H), 6.93 (d,  $J = 6.1$  Hz, 1H), 6.13 (d,  $J = 6.1$  Hz, 1H), 5.27 (s, 2H), 4.04 (s, 3H); ESI MS  $m/z$  481 [ $\text{C}_{26}\text{H}_{24}\text{N}_8\text{O}_2 + \text{H}$ ] $^+$

**7.3.703 (R920917): N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine**

A mixture of N4-(3-benzyloxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.20 g, 0.42 mmol) and 5% Pd/C (0.10 g) in 14:1 ethanol/concentrated hydrochloric acid (40 mL) was at room temperature was shaken in a hydrogen atmosphere at 50 psi. After 3 h no further hydrogen uptake was observed. The reaction mixture was filtered through diatomaceous earth, the solids washed with 95:5 methylene chloride/methanol and the filtrate concentrated to afford N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.16 g, 95%) as a tan solid:  $R_f$  0.23 (95:5 methylene chloride/methanol); mp (DSC) 207.1-212.8, 287.4-295.7 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  10.87 (br s, 1H), 10.81 (br s, 1H), 9.62 (br s, 1H), 8.08-8.06 (m, 1H), 7.72 (d,  $J$  = 9.0 Hz, 2H), 7.24 (br s, 1H), 7.20-7.00 (m, 3H), 6.61 (m, 2H), 6.46, (d,  $J$  = 6.0 Hz, 1H), 5.38 (s, 2H), 4.40 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  161.3, 160.1, 157.0, 154.3, 151.6, 141.7, 137.6, 129.1, 128.6, 123.4, 114.4, 111.9, 111.5, 108.3, 98.6, 59.6, 38.0; IR (ATR) 2975, 1639, 1602, 1521  $\text{cm}^{-1}$ ; ESI MS  $m/z$  391 [ $\text{C}_{19}\text{H}_{18}\text{N}_8\text{O}_2 + \text{H}$ ] $^+$ ; HPLC (Method A) 94.9 % (AUC),  $t_R$  = 8.19 min.

**7.3.704 N4-(3-Benzyloxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine [NEED R NO.]**

A mixture of N4-(3-benzyloxyphenyl)-2-chloro-4-pyrimidineamine (0.52 g, 1.69 mmol), 4-amino-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxybenzene (0.34 g, 1.69 mmol) and trifluoroacetic acid (0.4 mL) in 1-propanol (10 mL) was heated to 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride /methanol and purified by flash chromatography (95:5 methylene chloride /methanol) affording the requisite product N4-(3-benzyloxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a tan solid (0.41 g, 51%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  7.85 (d,  $J$  = 6.1 Hz, 1H), 7.49-7.04 (m, 14H), 6.93 (d,  $J$  = 9.0 Hz, 2H), 6.60-6.72 (m, 1H), 6.11 (d,  $J$  = 6.1 Hz, 1H), 5.14 (s, 2H), 4.34 (s, 3H); ESI MS  $m/z$  481 [ $\text{C}_{26}\text{H}_{24}\text{N}_8\text{O}_2 + \text{H}$ ] $^+$

**7.3.705 (R920910): N4-(3-Hydroxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine**

A mixture of N4-(3-benzyloxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.40 g, 0.42 mmol) and 5% Pd/C (0.10 g) in 14:1 ethanol/concentrated hydrochloric acid (40 mL) at room temperature was shaken in an

atmosphere of hydrogen at 50 psi. After 3 h no further hydrogen uptake was observed. The reaction mixture was filtered through diatomaceous earth, the solids washed with 95:5 methylene chloride/methanol and the filtrate concentrated to afford N4-(3-hydroxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.29 mg, 89%) as a beige solid:  $R_f$  0.43 (95:5 methylene chloride/methanol); mp 140-152 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  10.24 (br s, 1H), 9.98 (br s, 1H), 9.52 (br s, 1H), 7.94 (d,  $J$  = 6.6 Hz, 2H), 7.54 (d,  $J$  = 8.8 Hz, 2H), 7.43 (s, 1H), 7.26 (s, 1H), 7.18-7.01 (m, 3H), 6.53, (d,  $J$  = 7.5 Hz, 1H), 6.37, (d,  $J$  = 6.6 Hz, 1H), 5.52 (s, 2H), 4.13 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  160.2, 157.2, 154.5, 153.0, 151.2, 146.8, 139.9, 131.8, 128.7, 122.3, 114.7, 111.4, 110.5, 107.5, 99.5, 59.5, 33.3; IR (ATR) 3042, 1578, 1504, 1459  $\text{cm}^{-1}$ ; ESI MS  $m/z$  391  $[\text{C}_{19}\text{H}_{18}\text{N}_8\text{O}_2 + \text{H}]^+$ ; HPLC (Method A) 95.8 % (AUC),  $t_R$  = 8.82 min.

**7.3.706 (R920861): 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine**

A mixture of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (0.22 g, 0.93 mmol, 4-amino-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.19 g, 0.93 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated to 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) affording the requisite product 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.18 g, 49%):  $R_f$  0.47 (95:5 methylene chloride/methanol); mp 219-224 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.36 (s, 1H), 9.18 (s, 1H), 9.06 (s, 1H), 8.05 (d,  $J$  = 6.0 Hz, 1H), 7.60 (d,  $J$  = 9.0 Hz, 2H), 7.27 (d,  $J$  = 9.0 Hz, 1H), 7.09 (t,  $J$  = 8.0 Hz, 2H), 6.94 (d,  $J$  = 9.0 Hz, 2H), 6.49 (dd,  $J$  = 8.0, 2.1 Hz, 1H), 5.45 (s, 2H), 4.11 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  157.4, 155.5, 151.7, 151.6, 149.6, 149.5, 142.0, 142.0, 139.3 (d,  $J_{\text{C-F}}$  = 127.5 Hz), 135.3, 128.9, 120.1, 114.9, 112.3, 110.3, 108.5, 58.5, 33.9; IR (ATR) 3278, 1586, 1542, 1508  $\text{cm}^{-1}$ ; ESI MS  $m/z$  409  $[\text{C}_{19}\text{H}_{17}\text{FN}_8\text{O}_2 + \text{H}]^+$ ; HPLC (Method A) 98.2 % (AUC),  $t_R$  = 7.69 min. Anal. Calcd for  $\text{C}_{19}\text{H}_{17}\text{FN}_8\text{O}_2 \cdot 0.5 \text{H}_2\text{O}$ : C, 54.74; H, 4.23; N, 26.88. Found: C, 54.55; H, 4.02; N, 26.62.

**7.3.707 (R920860): 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine**

A mixture of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (0.31 g, 1.28 mmol), 4-amino-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.26 g, 1.28 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated at 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.20 g, 37 %):  $R_f$  0.63 (95:5 methylene chloride/methanol); mp 220-224 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.36 (s, 1H), 9.17 (s, 1H), 9.02 (s, 1H), 8.05 (d,  $J$  = 2.8 Hz, 1H), 7.57 (d,  $J$  = 9.1 Hz, 2H), 7.27 (d,  $J$  = 8.0 Hz, 1H), 7.10 (dt,  $J$  = 2.8, 8.0 Hz, 2H), 6.91 (d,  $J$  = 9.1 Hz, 2H), 6.49 (dd,  $J$  = 8.0, 2.8 Hz, 1H), 5.29 (s, 2H), 4.39 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  162.2, 157.4, 155.5, 152.1, 149.6, 149.5, 140.9 (d,  $J_{\text{C-F}}$  = 142.0 Hz), 140.5, 140.2, 138.7, 134.8, 128.9, 120.2, 114.5, 112.2, 110.2, 108.5, 60.5, 38.5; IR (ATR) 3274, 1587, 1507  $\text{cm}^{-1}$ ; ESI MS  $m/z$  409  $[\text{C}_{19}\text{H}_{17}\text{FN}_8\text{O}_2 + \text{H}]^+$ ; HPLC (Method A) 97.2 % (AUC),  $t_R$  = 8.04 min. Anal. Calcd for  $\text{C}_{19}\text{H}_{17}\text{FN}_8\text{O}_2$ : C, 55.88; H, 4.20; N, 27.44. Found: C, 55.56; H, 4.10; N, 27.17.

**7.3.708 (R920894): N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine**

A mixture of 2-chloro-N4-(3-hydroxyphenyl)-5-methyl-4-pyrimidineamine (0.20 g, 0.85 mmol), 4-amino-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.17 g, 0.85 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated at 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give N4-(3-hydroxyphenyl)-5-methyl-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.18 g, 52%):  $R_f$  0.61 (95:5 methylene chloride/methanol); mp 209-211 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.30 (s, 1H), 8.82 (s, 1H), 8.13 (s, 1H), 7.83 (s, 1H), 7.60 (d,  $J$  = 9.0 Hz, 2H), 7.18-7.05 (m, 3H), 6.89 (d,  $J$  = 9.0 Hz, 2H), 6.48 (t,  $J$  = 7.1 Hz, 1H), 5.27 (s, 2H), 4.39 (s, 3H), 2.08 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  161.7, 158.6, 157.5, 156.7, 154.7, 151.2, 140.2, 134.6, 134.6, 128.1, 119.3, 114.0, 112.6, 109.4, 108.9,



104.7, 59.8, 38.0, 12.9; IR (ATR) 3003, 1602, 1581, 1531, 1507  $\text{cm}^{-1}$ ; ESI MS  $m/z$  405  $[\text{C}_{20}\text{H}_{20}\text{N}_8\text{O}_2 + \text{H}]^+$ ; HPLC (Method A) 96.8 % (AUC),  $t_R$  = 8.23 min.

**7.3.709 (R920893): N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine**

A mixture of 2-chloro-N4-(3-hydroxyphenyl)-5-methyl-4-pyrimidineamine (0.20 g, 0.85 mmol), 4-amino-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.17 g, 0.85 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated at 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.14 g, 42%);  $R_f$  0.44 (95:5 methylene chloride/methanol); mp 219-221 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.32 (s, 1H), 8.85 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.64 (d,  $J$  = 9.0 Hz, 2H), 7.20-7.07 (m, 3H), 6.91 (d,  $J$  = 9.0 Hz, 2H), 6.50 (dd,  $J$  = 8.0, 1.2 Hz, 1H), 5.45 (s, 2H), 4.12 (s, 3H), 2.09 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  158.0, 157.0, 156.1, 154.3, 150.6, 150.0, 139.6, 134.6, 127.5, 118.6, 113.7, 112.0, 108.8, 108.2, 104.2, 57.4, 32.7, 12.3; IR (ATR) 3428, 1595, 1567, 1509  $\text{cm}^{-1}$ ; ESI MS  $m/z$  405  $[\text{C}_{20}\text{H}_{20}\text{N}_8\text{O}_2 + \text{H}]^+$ ; HPLC (Method A) 98.5 % (AUC),  $t_R$  = 7.89 min. Anal. Calcd for  $\text{C}_{20}\text{H}_{20}\text{N}_8\text{O}_2 \cdot \text{H}_2\text{O}$ : C, 57.00; H, 5.02; N, 26.59. Found: C, 56.86; H, 4.92; N, 26.50.

**7.3.710 N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-(1,2,3,4-tetrazol-5-yl)-2,4-pyrimidinediamine (R925810)**

In a manner similar to experiment #, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and sodium azide were reacted to yield N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-(1,2,3,4-tetrazol-5-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 25.8 min.; purity: 95%; MS: 535 ( $\text{MH}^+$ ).

**7.3.711 N2-[4-(N-Cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925838)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with cyclopropylmethylamine gave N2-[4-(N-

cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: MS (m/e): 478 (MH<sup>+</sup>).

5                   **7.3.712    5-Ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925839)**

                  In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyridinediamine with methylamine hydrochloride gave 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: MS (m/e): 438 (MH<sup>+</sup>).

**7.3.713    N2-[4-(N-2,3-Dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925840)**

15               In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyridinediamine with 3-amino-1,2-propanediol gave N2-[4-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: MS (m/e): 498 (MH<sup>+</sup>).

**7.3.714    N2,N4-Bis[4-[N-(3-methoxybenzylamino)carbonylmethyleneoxy]phenyl]-5-bromo-2,4-pyrimidinediamine (R925841)**

25               In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2,N4-bis[4-ethoxycarbonylmethyleneoxyphenyl]-5-bromo-2,4-pyrimidinediamine with 3-methoxybenzylamine gave N2,N4-bis[4-[N-(3-methoxybenzylamino)carbonylmethyleneoxy]phenyl]-5-bromo-2,4-pyrimidinediamine. LCMS: ret. time: 25.94 min.; purity: 95 %; MS (m/e): 727 (MH<sup>+</sup>).

**7.3.715 5-Bromo-N4-[4-[(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925842)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-bromo-N4-(4-ethoxycarbonylmethyleneoxyphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine with cyclopropylmethylamine gave 5-bromo-N4-[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 20.63 min.; purity: 100 %; MS (m/e): 485 (MH<sup>+</sup>).

**7.3.716 5-Bromo-N2-(3-hydroxyphenyl)-N4-[4-(N-3-methoxybenzylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925843)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-bromo-N4-(4-ethoxycarbonylmethyleneoxyphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine with 3-methoxybenzylamine gave 5-bromo-N2-(3-hydroxyphenyl)-N2-(3-hydroxyphenyl)-N4-[4-(N-3-methoxybenzylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 22.34 min.; purity: 90 %; MS (m/e): 551 (MH<sup>+</sup>).

**7.3.717 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-carboxybenzofuran-5-yl)-2,4-pyrimidinediamine (R926698)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(2,3-dihydro-2-carboxybenzofuran-5-yl)-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and LiOH were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-carboxybenzofuran-5-yl)-2,4-pyrimidinediamine.

**7.3.718 N2,N4-Bis(4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926016)**

In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-trifluoromethylaniline gave N2,N4-bis(4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.06 (bs, 1H), 7.75 (d, 2H, J= 9 Hz), 7.67 (d, 2H, J= 9Hz), 7.63 (d, 2H, J= 9Hz), 7.54 (d, 2H, J= 9 Hz), 7.19 (bs, 1H), 6.96 (s, 1H); <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ -17598 (s, 3F), -17676 (s, 3F), -46549 (s, 1F); HPLC: 85% pure.

**7.3.719 N2-(3,4-Ethylenedioxyphenyl)-N4-(3,4-methylenedioxyphenylhydrazinyl)-5-fluoro-2-pyrimidineamine (R926406)**

In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro N4-(3,4-methylenedioxyphenylhydrazinyl)-4-pyrimidineamine with 3,4-ethylenedioxyaniline gave N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3,4-methylenedioxyphenylhydrazinyl)-2-pyrimidineamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.82 (d, 1H, J= 3.6 Hz), 7.52 (dd, 1H, J= 1.8 and 7.5 Hz), 7.40 (d, 1H, J= 1.2 Hz), 7.14 (d, 1H, J= 2.4 Hz), 6.92 (d, 1H, J= 8.4 Hz), 6.85 (dd, 1H, J= 2.1 and 8.7 Hz), 6.45 (d, 1H, J= 9Hz), 6.06 (s, 2H), 4.10 (s, 4H); LCMS: ret. time: 12.14 min.; purity: 88%; MS (m/e): 426 (MH<sup>+</sup>).

**7.3.720 N2,N4-Bis(4-ethoxycarbonylmethylenedioxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine (R926566)**

To a solution of 2,4-dichloro-5-nitropyrimidine (0.264 g, 1 mmol) in EtOAc (10 mL) at 0 °C was added diisopropylethyl amine (0.200 mL) followed by ethyl 4-aminophenoxy acetate (0.585 g, 3 mmol) and then shaken at room temperature for 2h. The reaction was quenched with water and extracted with EtOAc. The EtOAc extract was washed with 2N HCl and water. The solvent was evaporated and the residue was purified by crystallization using EtOAc/hexanes to afford N2,N4-bis(4-ethoxycarbonylmethylenedioxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine (R926566). <sup>1</sup>H NMR (CDCl<sub>3</sub>): 10.32 (s, 1H), 7.42 (s, 1H), 7.40 (d, 2H, J= 8.7 Hz), 7.32 (d, 2H, J= 8.7 Hz), 6.93 (d, 2H, J= 8.7 Hz), 6.82 (d, 2H, J= 8.7 Hz), 4.67 (s, 2H), 4.62 (s, 2H), 4.47 (q, 2H, J= 7.5 Hz), 4.30 (m, 4H), 1.42 (t, 3H, J= 6.9 Hz), 1.31 (m, 6H); LCMS: ret. time: 32.10 min.; purity: 100%; MS (m/e): 584 (MH<sup>+</sup>).

**7.3.721 N2,N4-Bis[2-(methylthio)-1,3-benzothiaz-6-yl]-5-fluoro-2,4-pyrimidinediamine (R950202)**

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine and 2-(methylthio)-1,3-benzothiazol-6-amine were reacted to prepare N2,N4-bis[2-(methylthio)-1,3-benzothiaz-6-yl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 24.98 min.; purity: 84.6%; MS (m/e): 486.80 (MH<sup>+</sup>).

**7.3.722 N4-[3-(2-Hydroxyethyleamino)phenyl]-N2-[3-(N-(N-methyl)-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950240)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N-methylpiperazine were reacted to give N4-[3-(2-hydroxyethylenoxy)phenyl]-N2-[3-(N-(N-methyl)-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.36 min.; purity: 97.6%; MS (m/e): 495.42 (MH<sup>+</sup>).

**7.3.723 N4-[3-(2-Hydroxyethyleamino)phenyl]-N2-[3-(N-piperazino)-carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950241)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethyleneamino)phenyl]-2,4-pyrimidinediamine and piperazine were reacted to give N4-[3-(2-hydroxyethyleneamino)phenyl]-N2-[3-(N-piperazino)-carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.21 min.; purity: 100%; MS (m/e): 481.40 (MH<sup>+</sup>).

**7.3.724 (±)-N4-(3-Aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-D,L-N-phtaloylamino)propylenecarbonylaminophenyl]-2,4-pyrimidinediamine (R950251)**

N2,N4-Bis(4-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and N-phtaloyl-DL-glutamic anhydride were reacted in DMF to give N4-(3-aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-D,L-N-phtaloylamino)propylenecarbonylaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 19.41 min.; purity: 95.7%; MS (m/e): 569.98 (MH<sup>+</sup>).

**7.3.725 (±)-N4-(3-Aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-amino)propylenecarbonylaminophenyl]-2,4-pyrimidinediamine (R950255)**

(±)-N4-(3-Aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-D,L-N-phtaloylamino)propylenecarbonylaminophenyl]-2,4-pyrimidinediamine was reacted with hydrazine to give N4-(3-aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-

amino)propylenecarbonylamino]phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 11.98 min.; purity: 90.1%; MS (m/e): 440.3 (MH<sup>+</sup>).

**7.3.726 5-Methoxycarbonyl-N2,N4-bis[4-(N-pyrrolidino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926559)**

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In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with pyrrolidine gave 5-methoxycarbonyl-N2,N4-bis[4-(N-pyrrolidino) methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. The ethyl ester at 5-position was exchanged to methyl ester in methanol as a solvent. MS (m/e): 575 (MH<sup>+</sup>).

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**7.3.727 N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyridinediamine (R925565)**

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with ethyl 4-aminophenoxyacetate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyridinediamine. MS (m/e): 485 (MH<sup>+</sup>).

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**7.3.728 N2-(3-Ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(3,4-tetrafluoroethylenedioxyphenyl)-2,4-pyrimidinediamine (R926799)**

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In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of ethyl 3-aminophenoxyacetate with 2-chloro-5-ethoxycarbonyl-N4-(3,4-tetrafluoroethylenedioxyphenyl)-4-pyrimidineamine gave N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(3,4-tetrafluoroethylenedioxyphenyl)-2,4-pyrimidinediamine. MS (m/e): 567 (MH<sup>+</sup>).

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**7.3.729 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[N-2-(D)-(+)-biotinylethylamino]carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926811)**

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To a solution of D-(+)-biotin and N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DMF at -20 °C was added diisopropylethylamine and the mixture was shaken for 10 minutes. To this mixture was added benzotriazole-1-yl-oxy-tris(dimethylamino)-

phosphoniumhexafluorophosphate (BOP) and shaken at room temperature for 24 h. The reaction was quenched with water and extracted with ethyl acetate. The ethyl acetate extract was washed with aqueous solution of NaHCO<sub>3</sub> and finally with water. The residue obtained after the removal of solvent was purified by preparative TLC to obtain the desired  
5 N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[N-2-(D)-(+)-biotinylethylamino] carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 19.29 min.; purity: 99%; MS (m/e): 682 (M<sup>+</sup>).

**7.3.730 5-Fluoro-N4-(3-hydroxyphenyl)-N2[2-(N-methyl-N-2-hydroxyethyl)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926725)**

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In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2[2-methoxycarbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with 2-(N-methyl)ethanolamine gave 5-fluoro-N4-(3-hydroxyphenyl)-  
15 N2[2-(N-methyl-N-2-hydroxyethyl)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.87 min.; purity: 98%; MS: 438 (MH<sup>+</sup>).

**7.3.731 N2,N4-Bis(3-ethoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926228)**

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In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine and 3-ethoxycarbonylaniline gave N2,N4-bis(3-ethoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 26.55 min.; purity: 100%; MS (m/e): 425 (MH<sup>+</sup>).

**7.3.732 N2-(3-chloro-4-methylbenzyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R908696)**

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In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2-chloro-N4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 3-chloro-4-methylbenzylamine gave N2-(3-chloro-4-methylbenzyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 25.38 min.; purity: 99 %; MS (m/e): 401 (MH<sup>+</sup>).

**7.3.733 (+)-N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-phenylethyl)-2,4-pyrimidinediamine (R908697)**

In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2-chloro-N4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with (+)-2-aminoethylbenzene gave (+)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-phenylethyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.48 min.; purity: 99 %; MS (m/e): 367 (MH<sup>+</sup>).

**7.3.734 N2-(3-Ethoxycarbonylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R925745)**

In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-ethoxycarbonylaniline gave N2-(3-ethoxycarbonylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.04 (bs, 1H), 7.94 (bs, 1H), 7.90 (bd, 1H), 7.68 (bd, 1H, J= 7.5 Hz), 7.35 (t, 1H, J= 8.1 Hz), 7.28 (d, 1H, J= 2.4 Hz), 7.07 (s, 1H), 6.93 (dd, 1H, J= 3 and 8.7 Hz), 6.83 (d, 1H, J= 9 Hz), 6.64 (bs, 1H), 4.36 (q, 2H, J= 7.2 Hz), 4.26 (s, 4H), 1.35 (t, 3H, J= 7.5 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>): -47247; LCMS: ret. time: 15.88.; purity: 100%; MS (m/e): 411 (MH<sup>+</sup>).

**7.3.735 N4-(3,4-Difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920394)**

A solution of N-methyl 3-aminophenoxyacetamide (1 equivalent) and 2-chloro-N4-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine (1.2 equivalents) in MeOH was shaken in a sealed tube at 100 °C for 24 hours for 24 h. Upon cooling to the room temperature, it was diluted with ethyl acetate. The resulting solid was filtered and washed with a mixture of ethyl acetate: n-hexanes (1:1; v/v) to obtain N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.05 (bs, 1H), 9.83 (bs, 1H), 8.23 (d, 1H, J= 2.7 Hz), 7.98 (m, 2H), 7.52 (m, 1H), 7.39 (m, 1H), 7.20 (m, 3H), 6.60 (m, 1H), 4.37 (s, 2H), 2.63 (d, 3H, J= 3.3 Hz); LCMS: purity: 94%; MS (m/e): 404 (MH<sup>+</sup>).



**7.3.736 N4-(4-Chlorophenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920396)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.21 (bs, 1H), 10.00 (bs, 1H), 8.26 (d, 1H, J= 4.8 Hz), 8.00 (bd, 1H, J= 4.2 Hz), 7.77 (dd, 2H, J= 2.1 and 7.6 Hz), 7.37 (dd, 2H, J= 2.1 and 7.6 Hz), 7.17 9m, 3H), 8.63 (dd, 1H, J= 1.8 and 8.1 Hz), 4.37 (s, 2H), 2.64 (d, 3H, 4.5 Hz); LCMS: purity: 92%; MS (m/e): 402 (MH<sup>+</sup>).

**7.3.736.1 N4-(3,4-Dichlorophenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920397)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-dichlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.02 (bs, 1H), 9.76 (bs, 1H), 8.24 (d, 1H, J= 4.2 Hz), 8.08 (m, 1H), 7.97 (bd, 1H, J= 4.8 Hz), 7.77 (m, 1H), 7.55 (d, 1H, J= 8.7 Hz), 7.18 (m, 3H), 6.58 (m, 1H), 4.36 (s, 1H), 2.63 (d, 1H, J= 2.7 Hz); LCMS: purity: 91%; MS: 434 (MH<sup>+</sup>).

**7.3.737 5-Fluoro-N4-(5-methylpyridin-2-yl)-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920398)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(5-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N4-(5-methylpyridin-2-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 11.35 (bs, 1H), 10.70 (bs, 1H), 8.58 (s, 1H), 8.42 (d, 1H, J= 3.0 Hz), 8.12 (bd, 1H, J= 9.3 Hz), 8.03 (bd, 1H, J= 4.2 Hz), 7.82 (d, 1H, J= 8.7 Hz), 7.56 (s, 1H), 7.30 (bdd, 1H, J= 8.1

Hz), 7.19 (t, 1H, J= 8.1 Hz), 6.55 (dd, 1H, J= 1.8 and 8.1 Hz), 4.41 (s, 2H), 2.63 (d, 3H, J= 3.6 Hz), 2.36 (s, 3H); LCMS: purity: 99%; MS (m/e): 382 (M<sup>+</sup>).

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7.3.738    **5-Fluoro-N4-(6-methylpyridin-2-yl)-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920399)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(6-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N4-(6-methylpyridin-2-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  
10    δ 10.00 (bs, 1H), 9.60 (bs, 1H), 8.25 (s, 1H), 7.95 (m, 3H), 7.30 (s, 1H), 7.10 (m, 3H), 6.55 (d, 1H, J= 7.2 Hz), 4.40 (s, 2H), 2.62 (d, 3H, J= 3.6 Hz), 2.45 (s, 3H); LCMS: purity: 92%; MS (m/e): 383 (MH<sup>+</sup>).

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7.3.739    **N4-(5-Chloropyridin-2-yl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920405)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(5-chloropyridin-2-yl)-5-fluoro-4-pyrimidineamine gave N4-(5-chloropyridin-2-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  
20    δ 10.04 (bs, 1H), 9.53 (bs, 1H), 8.40 (d, 1H, J= 2.4 Hz), 8.22 (m, 2H), 7.88 (bd, 1H, J= 4.5 Hz), 7.86 (dd, 1H, J= 2.4 and 8.7 Hz), 7.40 (d, 1H, J= 1.8 Hz), 7.19 (m, 2H), 6.51 (bdd, 1H, J= 1.2 and 9 Hz), 4.38 (s, 2H), 2.64 (d, 3H, J= 3.3 Hz); LCMS: purity: 95%; MS (m/e): 403  
25    (MH<sup>+</sup>).

7.3.740    **N4-(6-Chloropyridin-3-yl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920406)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(6-chloropyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(6-chloropyridin-3-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  
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$\delta$  9.72 (s, 1H), 9.38 (s, 1H), 8.93 (t, 1H, J= 3.0 Hz), 8.28 (m, 1H), 8.18 (d, 1H, J= 3.6 Hz), 7.95 (m, 1H), 7.45 (d, 1H, J= 8.7 Hz), 7.39 (m, 1H), 7.21 (m, 1H), 7.14 (t, 1H, J= 4.8 Hz), 6.50 (bdd, 1H, J= 7.8 Hz), 4.4 (s, 2H), 2.63 (d, 3H); LCMS: purity: 100%; MS (m/e): 403 (MH<sup>+</sup>).

5                                **7.3.741    5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(4-methylpyridin-2-yl)-2,4-pyrimidinediamine (R927016)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(4-methylpyridin-2-yl)-2,4-pyrimidinediamine. LCMS: purity: 95%; MS (m/e): 383 (MH<sup>+</sup>).

15                                **7.3.742    5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R920407)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  9.835 (bs, 1H), 9.54 (bs, 1H), 8.20 (d, 1H, J= 3.6 Hz), 7.94 (m, 2H), 7.78 (bs, 1H), 7.43 (t, 1H, J= 8.4 Hz), 7.25 (m, 2H), 7.15 (t, 1H, J= 7.5 Hz), 7.03 (bd, 1H, J= 9.3 Hz), 6.55 (bd, 1H, J= 7.5 Hz), 4.36 (s, 2H), 2.63 (d, 3H, J= 4.5 Hz); LCMS: purity: 91%; MS (m/e): 452 (MH<sup>+</sup>).

25                                **7.3.743    N4-(3,4-Difluoromethylenedioxyphenyl)-5-fluoro- N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920408)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro- N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  9.91 (bs, 1H), 9.64 (bs, 1H), 8.19 (d, 1H, J= 3.9 Hz), 8.03 (s, 1H), 7.96 (bd, 1H, J= 4.8 Hz), 7.46 (m, 1H), 7.36 (d, 1H, J= 8.7 Hz), 7.27 (bs, 1H), 7.17 (m, 2H), 6.57 (bdd, 1H,

J= 7.2 Hz), 4.36 (s, 1H), 2.62 (d, 3H, J= 4.5 Hz); LCMS: purity: 96%; MS (m/e): 448 (MH<sup>+</sup>).

5                    **7.3.744    N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920410)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.08 (d, 1H, J= 5.4 Hz), 7.99 (d, 1H, J= 3.6 Hz), 7.67 (dd, 1H, J= 2.4 and 9.0 Hz), 7.40 (m, 3H), 7.06 (m, 2H), 6.92 (dd, 1H, J= 2.4 and 8.4 Hz), 4.44 (s, 2H), 2.80 (s, 3H); <sup>19</sup>F NMR (CD<sub>3</sub>OD): - 16973 and - 45983; LCMS: purity: 96%; MS (m/e): 486 (MH<sup>+</sup>).

15                    **7.3.745    N4-(4-Ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926827)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 96%; MS: 412 (MH<sup>+</sup>).

25                    **7.3.746    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926828)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-amino-6-methoxyphenoxyacetamide with 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.83 (s, 1H), 7.80 (d, 1H, J= 4.2 Hz), 7.30 (d, 1H, 2.4 Hz), 7.23 (d, 1H, J= 2.4 Hz), 7.06 (m, 2H), 6.90 (d, 1H, J= 5.7 Hz), 6.73 (d, 1H, J= 5.2

Hz), 4.32 (s, 2H), 4.22 (s, 4H), 3.86 (s, 3H), 2.83 (s, 3H); LCMS: purity: 97%; MS (m/e): 455 (MH<sup>+</sup>).

5                   **7.3.747    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926829)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-amino-4-methoxyphenoxyacetamide with 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.86 (d, 1H, J= 4.2 Hz), 7.35 (d, 1H, J= 2.4 Hz), 7.19 (m, 1H), 7.12 (m, 3H), 6.93 (d, 1H, J= 8.7 Hz), 6.52 (m, 1H), 4.37 (s, 2H), 3.85 (s, 3H), 2.82 (s, 3H); <sup>19</sup>F NMR (CD<sub>3</sub>OD): - 47650; LCMS: purity: 100%; MS: 414 (MH<sup>+</sup>).

15                   **7.3.748    N4-(3-Chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926832)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of 3 N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3-chlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(3-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.12 (s, 1H), 9.93 (s, 1H), 8.27 (d, 1H, J= 4.2 Hz), 7.98 (d, 1H, J= 4.9 Hz), 7.85 (s, 1H), 7.73 (d, 1H, J= 8.1 Hz), 7.35 (t, 1H, J= 8.4 Hz), 7.19 (m, 3H), 6.62 (m, 1H), 4.36 (s, 2H), 2.63 (d, 3H, J= 4.2 Hz); LCMS: purity: 95%; MS: 402 (MH<sup>+</sup>).

25                   **7.3.749    5-Fluoro-N4-(3-methoxy-5-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926833)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-methoxy-5-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(3-methoxy-5-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 95%; MS (m/e): 466 (MH<sup>+</sup>).

**7.3.750 5-Fluoro-N4-(3-hydroxy-4-methoxyphenyl)-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926834)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-hydroxy-4-methoxyphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(3-hydroxy-4-methoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.70 (bs, 2H), 8.12 (d, 1H, J= 4.8 Hz), 7.96 (m, 1H), 7.12 (m, 5H), 6.85 (d, 1H, J= 8.7 Hz), 6.57 (bd, 1H, J= 8.1 Hz), 4.35 (s, 2H), 3.74 (s, 3H), 2.63 (d, 3H, J= 4.5 Hz); LCMS: purity: 99%; MS (m/e): 414 (MH<sup>+</sup>).

**7.3.751 5-Fluoro-N4-(4-methoxy-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926835)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-methoxy-3-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(4-methoxy-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.9 Bs, 1H), 9.62 (bs, 1H), 8.17 (d, 1H, J= 4.2 Hz), 8.04 (bdd, 1H, J= 7.2 Hz), 7.82 (t, 1H, 2.7 Hz), 7.18 (m, 3H), 7.11 (t, 1H, J= 8.1 Hz), 6.55 (bd, 1H, J= 6.9 Hz); 4.33 (s, 2H), 3.86 (s, 3H), 2.61 (d, 3H, J= 4.0 Hz); LCMS: purity: 93%; MS: 466 (MH<sup>+</sup>).

**7.3.752 5-Fluoro-N4-(4-fluoro-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926838)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-fluoro-3-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(4-fluoro-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.80 (s, 1H), 9.44 (s, 1H), 8.25 (m, 1H), 8.18 (d, 1H, J= 3.9 Hz), 8.00 (m, 1H), 7.97 (m, 1H), 7.47 (t, 1H, J= 9.6 Hz), 7.26 (s, 1H), 7.21

(m, 1H), 7.11 (t, 1H, J= 8.4 Hz), 6.51 (bd, 1H, J= 9.9 Hz), 4.34 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 88%; MS: 454 (MH<sup>+</sup>).

5                    **7.3.753    N4-(3-Chloro-4-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926839)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3-chloro-4-methylphenyl)-4-pyrimidineamine gave N4-(3-chloro-4-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d6): δ 9.69 (s, 1H), 9.52 (s, 1H), 8.16 (d, 1H, J= 4.2 Hz), 7.96 (bs, 1H), 7.81 (d, 1H, J= 2.1 Hz), 7.67 (bd, 1H, J= 8.4 Hz), 7.26 (m, 3H), 7.15 (t, 1H, J= 8.1 Hz), 6.54 (bd, 1H, J= 7.2 Hz), 4.34 (s, 2H), 2.63 (d, 3H, J= 4.2 Hz), 2.27 (s, 3H); LCMS: purity: 80%; MS (m/e): 415 (M<sup>+</sup>).

15                    **7.3.754    N4-(2-Chloro-5-methylphenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926840)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(2-chloro-5-methylphenyl)-4-pyrimidineamine gave N4-(2-chloro-5-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d6): δ 9.80 (bs, 2H), 8.21 (d, 1H, J= 4.8 Hz), 7.92 (d, 1H, J= 4.8 Hz), 7.46 (m, 1H), 7.31 (m, 2H), 7.04 (m, 2H), 6.53 (bd, 1H, J= 8.1 Hz), 4.30 (s, 1H), 2.18 (s, 3H); LCMS: purity: 93%; MS (m/e): 416 (MH<sup>+</sup>).

25                    **7.3.755    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-isopropylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926830)**

The reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(ethoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with isopropylamine (5 equivalents) in the presence of diisopropylethylamine (5 equivalents) in MeOH in a sealed tube at 80 °C for 24 hours gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-isopropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-

d6):  $\delta$  9.15 (s, 1H), 8.04 (d, 1H,  $J$  = 4.2 Hz), 7.77 (d, 1H,  $J$  = 7.5 Hz), 7.28 (m, 4H), 7.08 (t, 1H,  $J$  = 8.1 Hz), 6.78 (d, 1H,  $J$  = 8.7 Hz), 6.45 (dd, 1H,  $J$  = 1.8 and 7.8 Hz), 4.30 (s, 2H), 4.20 (s, 4H), 3.92 (m, 1H), 1.06 (d, 6H,  $J$  = 6.6 Hz); LCMS: purity: 95%; MS (m/e): 454 ( $MH^+$ ).

5                                    **7.3.756    N2-[3-(N-Cyclopropylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926848)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-isopropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(ethoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with cyclopropylamine gave 5-fluoro-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(N-cyclopropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine.  $^1H$  NMR (DMSO-d6):  $\delta$  9.17 (bs, 2H), 8.05 (m, 2H), 7.27 (m, 4H), 7.08 (t, 1H,  $J$  = 8.1 Hz), 7.67 (d, 1H,  $J$  = 8.7 Hz), 6.42 (dd, 1H,  $J$  = 2.4 and 8.1 Hz), 4.3 (s, 2H), 4.2 (bs, 4H), 2.65 (m, 1H), 0.6 (m, 2H), 0.45 (m, 2H); LCMS: purity: 91%; MS (m/e): 452 ( $MH^+$ ).

15                                    **7.3.757    N4-(4-Cyano-3-methylphenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926851)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-cyano-3-methylphenyl)-4-pyrimidineamine gave N4-(4-cyano-3-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine.  $^1H$  NMR (DMSO-d6):  $\delta$  9.7 (s, 1H), 9.40 (s, 1H), 8.2 (s, 1H), 8.00-7.50 (m, 3H), 7.40-7.00 (m, 3H), 6.50 (bm, 1H), 4.35 (s, 2H), 2.60 (s, 3H), 2.35 (s, 3H); LCMS: purity: 91%; MS (m/e): 407 ( $MH^+$ ).

25                                    **7.3.758    5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926855)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine.  $^1H$  NMR (DMSO-d6):  $\delta$  10.04 (bs, 1H), 9.65 (bs, 1H), 8.35 (s, 1H), 8.23 (d, 1H,  $J$  = 3.9 Hz), 8.00 (bd, 1H,  $J$  = 6.6 Hz), 7.91 (bd,



J= 3.6 Hz), 7.77 (d, 1H, J= 8.1 Hz), 7.57 (t, 1H, J= 8.1 Hz), 7.23 (m, 2H), 6.95 (t, 1H, J= 8.4 Hz), 6.46 (bdd, 1H, J= 1.8 and 8.1 Hz), 4.22 (s, 2H), 2.62 (d, 3H, 4.2 Hz); LCMS: purity: 83%; MS (m/e): 436 (MH<sup>+</sup>).

5                    **7.3.759    5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(N-methylphthalimido-4-yl)-2,4-pyrimidinediamine (R926856)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(N-methylphthalimido-4-yl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(N-methylphthalimido-4-yl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.95 (s, 1H), 9.44 (s, 1H), 8.29 (m, 1H), 8.25 (m, 1H), 8.18 (d, 1H, J= 1.8 Hz), 7.88 (bd, 1H, J= 4.5 Hz), 7.75 (d, 1H, J= 6.6 Hz), 7.38 (bs, 1H), 7.22 (bd, 1H, J= 8.1 Hz), 7.14 (t, 1H, J= 7.8 Hz), 6.50 (dd, 1H, J= 1.8 and 9.0 Hz), 4.28 (s, 2H), 2.99 (s, 3H), 2.60 (d, 3H, J= 4.5 Hz); LCMS: purity: 92%; MS (m/e): 451 (MH<sup>+</sup>).

**7.3.760    N4-(2,5-Dimethoxy-4-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926859)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with N4-(2,5-dimethoxy-4-chlorophenyl)-2-chloro-5-fluoro-4-pyrimidineamine gave N4-(2,5-dimethoxy-4-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.05 (d, 1H, J= 5.4 Hz), 7.29 (s, 1H), 7.24 (t, 1H, J= 8.1 Hz), 7.18 (s, 1H), 7.02 (t, 1H, J= 2.1 Hz), 6.92 (dd, 1H, J= 1.8 and 8.1 Hz), 6.83 (dd, 1H, J= 2.4 and 8.4 Hz), 4.29 (s, 2H), 3.81 (s, 3H), 3.59 (s, 3H), 2.81 (s, 3H); LCMS: purity: 96%; MS (m/e): 460 (MH<sup>-</sup>); 462 (MH<sup>-</sup>).

**7.3.761    5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926862)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-methoxycarbonyl-5-

trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.95 (s, 1H), 9.41 (s, 1H), 8.57 (s, 1H), 8.33 (s, 1H), 8.23 (d, 1H, J= 3 Hz), 7.83 (s and d, 2H), 7.22 (m, 2H), 7.02(t, 1H, J= 8.7 Hz), 6.48 (1H, J= 2.4 and 7.5 Hz), 4.27 (s, 2H), 3.80 (s, 3H), 2.60 (d, 3H, J= 4.8 Hz); <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): - 17446; LCMS: purity: 94%; MS (m/z): 494 (MH<sup>+</sup>).

**7.3.762 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926870)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine. LCMS: purity: 86%; MS (m/e): 512 (MH<sup>+</sup>).

**7.3.763 N4-[3-(2-(3-Chlorophenyl)-1,3,4-oxadiazol-5-yl)phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926871)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[3-(2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl)phenyl]-4-pyrimidineamine gave N4-[3-(2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl)phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 100%; MS (m/e): 546 (MH<sup>+</sup>).

**7.3.764 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine (R926879)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-trifluoromethoxyphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.05 (bs, 1H), 9.74 (bd, 1H, J= 1.5 Hz), 8.22 (d, 1H, J= 4.2 Hz), 7.99 (bd, 1H, J= 4.5 Hz), 7.86 (m,

2H), 7.32 (d, 2H, J= 8.1 Hz), 7.26 (s, 1H), 7.16 (m, 2H), 6.58 (m, 1H), 4.36 (s, 2H), 2.65 (bd, 3H); LCMS: purity: 92%; MS (m/e): 452 (MH<sup>+</sup>).

5                    **7.3.765    5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-trifluoromethylphenyl]-2,4-pyrimidinediamine (R926880)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-trifluoromethylphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.10 (bs, 1H), 9.72 (d, 1H, J= 1.2 Hz), 8.26 (d, 1H, J= 4.2 Hz), 8.00 (m, 3H), 7.65 (d, 2H, J= 8.1 Hz), 7.31 (bs, 1H), 7.17 (d, 2H, J= 5.4 Hz), 6.59 (m, 1H), 4.36 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 92%; MS (m/e): 436 (MH<sup>+</sup>).

15                    **7.3.766    N4-(4-Chloro-3-trifluoromethylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926881)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-chloro-3-trifluoromethylphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chloro-3-trifluoromethylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.20 (bs, 1H), 9.81 (bs, 1H), 8.28 (d, 1H, J= 3.9 Hz), 8.23 (bdd, 1H, J= 8.7 Hz), 8.11 (d, 1H, J= 2.4 Hz), 7.98 (bd, 1H, J= 4.5 Hz), 7.65 (d, 1H, J= 8.7 Hz), 7.17 (m, 3H), 6.59 (m, 1H), 4.35 (s, 2H), 2.63 (d, 3H, J= 4.2 Hz); LCMS: purity: 87%; MS (m/e): 470 (MH<sup>+</sup>).

25                    **7.3.767    5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(quinolin-6-yl)-2,4-pyrimidinediamine (R926883)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of 3 N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(quinolin-6-yl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(quinolin-6-yl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.17 (bs, 1H), 9.83 (s, 1H), 8.24 (d, 1H, J= 4.8 Hz), 8.17 (m, 1H), 7.94 (m, 2H), 7.86 (m, 1H), 7.39 (d, 1H, J= 9.3

Hz), 7.25 (s, 1H), 7.16 (m, 2H), 6.60 (m, 1H), 6.50 (d, 1H, J= 9.6 Hz), 4.32 (s, 2H), 2.60 (d, 3H, J= 3.6 Hz); LCMS: purity: 98%; MS (m/e): 436 (MH<sup>+</sup>).

5                    **7.3.768    5-Fluoro-N4-(2-methoxypyridin-5-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926886)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(2-methoxypyridin-5-yl)-4-pyrimidineamine gave 5-fluoro-N4-(2-methoxypyridin-5-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.36 (bs, 1H), 9.19 (s, 1H), 8.59 (d, 1H, J= 3 Hz), 8.05 (m, 3H), 7.38 (m, 1H), 7.24 (bd, 1H, J= 8.1 Hz), 7.08 (t, 1H, J= 8.4 Hz), 6.79 (d, 1H, J= 8.7 Hz), 6.46 (dd, 1H, J= 2.4 and 7.8 Hz), 4.34 (s, 2H), 3.82 (s, 3H), 2.63 (d, 3H, J= 4.5 Hz); LCMS: purity: 95%; MS (m/e): 399 (MH<sup>+</sup>).

15                    **7.3.769    5-Fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927023)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-4-pyrimidineamine gave 5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.65 (bs, 1H), 9.45 (bs, 1H), 8.55 (s, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.99 (m, 2H), 7.28 (m, 1H), 7.19 (m, 2H), 7.11 (t, 1H, J= 8.4 Hz), 6.81 (d, 1H, J= 8.7 Hz), 6.52 (m, 2H), 4.35 (s, 2H), 4.23 (t, 2H, J= 5.1 Hz), 3.69 (t, 2H, J= 4.5 Hz), 2.63 (d, 3H, J= 2.7 Hz); LCMS: purity: 95%; MS (m/e): 429 (MH<sup>+</sup>).

30                    **7.3.770    N4-(2,6-Dimethoxypyridin-3-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920404)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-N2-[3-(N-

methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.05 (d, 1H, J= 1.8 Hz), 8.62 (s, 1H), 8.01 (d, 1H, J= 3.6 Hz), 7.91 (bd, 1H, J= 4.8 Hz), 7.77 (m, 1H), 7.18 (m, 2H), 6.96 (t, 1H, J= 8.1 Hz), 6.40 (d, 2H, J= 8.1 Hz), 4.29 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.63 (d, 3H, J= 4.5 Hz); LCMS: purity: 86%; MS (m/e): 429 (MH<sup>+</sup>).

**7.3.771 N4-(4-Chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927042)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.89 (bs, 1H), 9.66 (bs, 1H), 8.20 (d, 1H, J= 4.2 Hz), 7.95 (bd, 1H), 7.48 (m, 2H), 7.33 (d, 1H, J= 9.1 Hz), 7.26 (bs, 1H), 7.17 (m, 2H), 6.57 (bd, 1H, J= 7.8 Hz), 4.34 (s, 2H), 3.72 (s, 3H), 2.62 (d, 3H); LCMS: purity: 97%; MS (m/e): 432 (MH<sup>+</sup>).

**7.3.772 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R920411)**

A solution of 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine (1.1 equivalents) and 3-hydroxyaniline (1 equivalent) in a sealed tube was heated at 100 °C for 24 hours. The resulting solution was diluted with EtOAc and the solid obtained was filtered, washed with a mixture of EtOAc:n-hexanes (1:1; v/v), dried and analyzed to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.02 (d, 1H, J= 5.1 Hz), 7.98 (d, 1H, J= 3.0 Hz), 7.72 (dd, 1H, J= 3.0 and 9.3 Hz), 7.42 (dd, 1H, J= 1.2 and 9.0 Hz), 7.22 (t, 1H, J= 8.4 Hz), 6.85 (m, 2H), 6.73 (dd, 1H, J= 2.4 and 8.7 Hz); <sup>19</sup>F NMR (CD<sub>3</sub>OD): - 16967 and - 46027; LCMS: purity: 97%; MS (m/e): 415 (MH<sup>+</sup>).

**7.3.773 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[3-(3-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926866)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-5-fluoro-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-4-pyrimidineamine gave

5-fluoro-N2-(3-hydroxyphenyl)-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.72 (bs, 1H), 7.96 (bd, 3H), 7.85 (m, 2H), 7.56 (m, 4H), 7.14 (d, 1H, J= 2.1 Hz), 6.91 (m, 2H), 6.28 (dd, 1H, J= 1.8 and 6.9 Hz); LCMS: purity: 80%; MS (m/e): 441 (MH<sup>+</sup>).

5                                    **7.3.774    N4-(3,4-Difluoromethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926794)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-  
10 (3,4-difluoromethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: purity: 85%; MS (m/e): 377 (MH<sup>+</sup>).

**7.3.775    5-Fluoro-N2-(3-hydroxyphenyl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R926885)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with  
15 2-chloro-5-fluoro-N4-(3-trifluoromethoxyphenyl)-4-pyrimidineamine gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.99 (bs, 1H), 9.61 (bs, 1H), 8.21 (d, 1H, J= 4.2 Hz), 7.93 (bd, 1H, J= 7.5 Hz), 7.78 (s, 1H), 7.43 (t, 1H, J= 8.4 Hz), 7.03 (m, 4H), 6.43 (m, 1H); <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): -16097;  
20 LCMS: purity: 85%; MS (m/e): 381 (MH<sup>+</sup>).

**7.3.776    N4-(2,6-Dimethoxypyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926887)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with  
25 2-chloro-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.98 (bs, 2H), 8.20 (d, 1H, J= 5.4 Hz), 7.72 9m, 1H), 6.90 (t, 1H, J= 7.8 Hz), 6.81 (m, 2H), 6.42 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H); LCMS: purity: 94%; MS (m/e): 358 (MH<sup>+</sup>).

**7.3.777 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(5-methylpyridin-2-yl)-2,4-pyrimidinediamine (R927017)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with  
5 2-chloro-5-fluoro-N4-(5-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-(5-methylpyridin-2-yl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 11.39 (bs, 1H), 10.59 (bs, 1H), 8.58 (s, 1H), 8.41 (d, 1H, J= 3 Hz), 8.12 (d, 1H, J= 8.7 Hz), 7.82 (d, 1H, J= 8.7 Hz), 7.29 (s, 1H), 7.16 (d, 1H, J= 9 Hz), 7.05 (t, 1H, J= 8.4 Hz), 6.38 (dd, 1H, 1.2 and 6.9 Hz); LCMS: purity: 99%; MS (m/e): 312 (MH<sup>+</sup>).

**7.3.778 N4-(6-Chloropyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R927018)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with  
15 2-chloro-N4-(6-chloropyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(6-chloropyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.10 (bs, 1H), 9.64 (bs, 1H), 8.85 (m, 1H), 8.30 (m, 2H), 8.22 (d, 1H, J= 4.2 Hz), 7.43 (d, 1H, J= 8.7 Hz), 7.01 (m, 3H), 6.42 (bd, 1H, J= 8.4 Hz); LCMS: purity: 93%; MS (m/e): 332 (MH<sup>+</sup>).

**7.3.779 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(quinolin-6-yl)-2,4-pyrimidinediamine (R927019)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with  
25 2-chloro-5-fluoro-N4-(quinolin-6-yl)-4-pyrimidineamine gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-(quinolin-6-yl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.50 (s, 1H), 10.14 (s, 1H), 8.29 (d, 1H, J= 4.8 Hz), 8.14 (d, 1H, J= 1.8 Hz), 7.96 (d, 1H, J= 9.3 Hz), 7.83 (dd, 1H, J= 2.4 and 9.0 Hz), 7.40 (d, 1H, J= 8.7 Hz), 7.04 (t, 1H, J= 8.1 Hz), 6.93 (m, 2H), 6.52 (m, 2H); LCMS: purity: 93%; MS (m/e): 365 (MH<sup>+</sup>).

**7.3.780 N4-(5-Chloropyridin-2-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R927020)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with  
30 2-chloro-N4-(5-chloropyridin-2-yl)-5-fluoro-4-pyrimidineamine gave N4-(5-chloropyridin-

2-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.80 (bs, 1H), 9.77 (bs, 1H), 8.45 (bd, 1H), 8.26 (d, 1H, J= 3.9 Hz), 8.15 (d, 1H, J= 8.7 Hz), 7.85 (dd, 1H, J= 2.4 and 8.7 Hz), 7.06 (m, 3H), 6.43 (bd, 1H, J= 7.2 Hz); LCMS: purity: 97%; MS (m/e): 332 (MH<sup>+</sup>).

5                                    **7.3.781    N4-(4-Chloro-2,5-dimethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926860)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(4-chloro-2,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chloro-2,5-dimethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.96 (d, 1H, J= 4.8 Hz), 7.66 (s, 1H), 7.13 (s, 1H), 7.07 (t, 1H, J= 8.7 Hz), 8.86 (m, 2H), 6.57 (dd, 1H, J= 3.2 and 8.1 Hz), 3.48 (s, 3H), 3.66 (s, 3H); <sup>19</sup>F NMR (CD<sub>3</sub>OD): - 46968.

15                                    **7.3.782    N4-(4-Chlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine (R927026)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 5-amino-2-methoxycarbonylbenzofuran with 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.28 (bs, 1H), 10.18 (bs, 1H), 8.25 (d, 1H, J= 4.5 Hz), 7.96 (bs, 1H), 7.84 (m, 1H), 7.67 (m, 3H), 7.57 (m, 1H), 7.37 (bd, 2H, J= 9.0 Hz), 3.88 (s, 3H); LCMS: purity: 96%; MS (m/e): 413 (MH<sup>+</sup>).

25                                    **7.3.783    N4-(3,4-Dichlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine (R927027)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 5-amino-2-methoxycarbonylbenzofuran with 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-dichlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.70



(bs, 1H), 9.50 (bs, 1H), 8.20 (d, 1H, J= 4.5 Hz), 8.09 (m, 1H), 7.80 (m, 3H), 7.62 (m, 2H), 7.53 (m, 1H), 7.38 (m, 1H), 3.88 (s, 3H); LCMS: purity: 94%; MS (m/e): 448 (MH<sup>+</sup>).

**7.3.784 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926863)**

5 In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-methoxycarbonyl-5-trifluoromethylaniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.98 (s, 1H), 9.52 (s, 1H), 8.53 (s, 1H),  
10 8.38 (s, 1H), 8.20 (d, 1H, J= 4.2 Hz), 7.69 (s, 1H), 7.27 (d, 1H, J= 8.1 Hz), 7.14 (s, 1H), 7.05 (t, 1H, 7.8 Hz), 6.49 (dd, 1H, J= 1.8 and 8.4 Hz), 3.80 (s, 3H); LCMS: purity: 82%; MS (m/e): 423 (MH<sup>+</sup>).

**7.3.785 N2-(4-Chloro-2,5-dimethoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926857)**

15 In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 4-chloro-2,5-dimethoxyaniline gave N2-(4-chloro-2,5-dimethoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H  
NMR (CD<sub>3</sub>OD): δ 8.04 (d, 1H, J= 5.4 Hz), 7.46 (s, 1H), 7.17 (m, 2H), 7.03 (m, 2H), 6.72  
20 (dd, 1H, J= 1.8 and 7.8 Hz), 3.85 (s, 3H), 3.52 (s, 3H); LCMS: purity: 98%; MS (m/e): 390 (MH<sup>+</sup>).

**7.3.786 N2-(3-Bromo-5-trifluorophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926846)**

25 In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-bromo-5-trifluoromethylaniline gave N2-(3-bromo-5-trifluorophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H  
NMR (DMSO-d<sub>6</sub>): δ 9.70 (s, 1H), 9.36 (s, 1H), 9.34 (s, 1H), 8.31 (s, 1H), 8.18 (d, 1H, J= 3.6 Hz), 8.02 (s, 1H), 7.35 (s, 1H), 7.28 (bd, 1H, J= 7.2 Hz), 7.11 (t, 1H, J= 8.4 Hz), 7.02  
30 (m, 1H), 6.49 (dd, 1H, J= 1.8 and 7.8 Hz); LCMS: purity: 94%; MS (m/e): 442 (MH<sup>+</sup>).

**7.3.787 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(1H-pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine (R926841)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(1H-pyrazol-3-yl)aniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(1H-pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine. LCMS: purity: 84%; MS 363 (MH<sup>+</sup>)

**7.3.788 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926842)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(tetrazol-5-yl)aniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.05 (bs, 1H), 9.80 (bs, 1H), 8.27 (s, 1H), 8.23 (d, 1H, J= 3.3 Hz), 7.86 (d, 1H, J= 8.1 Hz) 7.65 (d, 1H, J= 6.9 Hz), 7.44 (t, 1H, J= 7.5 Hz), 7.19 (m, 2H), 6.93 (t, 1H, J= 7.5 Hz), 6.49 (dd, 1H, J= 2.4 and 8.1 Hz); LCMS: purity: 89%; MS (m/e): 364 (MH<sup>+</sup>).

**7.3.789 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(1,3-oxazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926831)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(1,3-oxazol-5-yl)aniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-(1,3-oxazol-5-yl)phenyl)-2,4-pyrimidinediamine. LCMS: purity: 76%; MS (m/e): 364 (MH<sup>+</sup>).

**7.3.790 N2-(3-Chloro-4-trifluoromethylphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinedimine (R926844)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-chloro-4-trifluoromethoxyaniline gave N2-(3-chloro-4-trifluoromethylphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinedimine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.70 (bs, 1H), 9.48 (bs, 1H), 8.15 (bd, 1H, J= 3.6 Hz), 8.06 (s, 1H), 7.62 (dd, 1H, J= 2.4 and 9.3 Hz), 7.37 (d, 1H, J= 9.0 Hz), 7.20 9m, 1H), 7.11 (m, 3H), 6.53 (bd, 1H, J= 8.1 Hz); LCMS: purity: 93%; MS (m/e): 414 (MH<sup>+</sup>).

**7.3.791 5-Fluoro-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926843)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 3-(tetrazol-5-yl)aniline gave 5-fluoro-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.91 (s, 1H), 9.74 (s, 1H), 8.29 (s, 1H), 8.18 (d, 1H, J= 4.5 Hz), 7.76 (bdd, 1H, J= 1.5 and 8.1 Hz), 7.64 (d, 1H, J= 8.1 Hz), 7.46 (t, 1H, J= 8.1 Hz), 7.29 (m, 1H), 7.13 (dd, 1H, J= 2.4 and 8.7 Hz), 6.64 (d, 1H, J= 8.7 Hz), 4.11 (m, 4H); LCMS: purity: 91%; MS (m/e): 407 (MH<sup>+</sup>).

**7.3.792 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-methoxy-2-methylphenyl)-2,4-pyrimidinediamine (R926845)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 4-methoxy-2-methylaniline gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-methoxy-2-methylphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.30 (bs, 1H), 9.10 (bs, 1H), 8.22 (d, 1H, J= 5.1 Hz), 7.55 (m, 1H), 7.15 (m, 1H), 7.07 (m, 1H), 6.92 (m, 2H), 6.82 (d, 1H, J= 8.7 Hz), 4.22 (bs, 4H), 3.80 (s, 3H), 2.15 (s, 3H); LCMS: purity: 94%; MS (m/e): 383 (MH<sup>+</sup>).

**7.3.793 N2-[5-(N-Aminocarbonylmethylene-2-oxo-1,3-oxazol-3(2H)-yl)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926847)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 2-[5-amino-2-oxo-1,3-benzoxazol-3(2H)-yl]acetamide gave N2-[5-(N-aminocarbonylmethylene-2-oxo-1,3-oxazol-3(2H)-yl)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.95 (d, 1H, J= 8.4 Hz), 7.32 (dd, 1H, J= 2.4 and 8.1 Hz), 7.24 (d, 1H, J= 2.4 Hz), 7.19 (m, 2H), 6.95 (dd, 1H, J= 2.7 and 9 Hz), 6.80 (d, 1H, J= 9 Hz), 4.51 (s, 2H), 4.21 (m, 4H).

**7.3.794 N2-[3-(2-Ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)phenyl-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926874)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)aniline gave N2-[3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)phenyl-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.52 (s, 1H), 9.31 (s, 1H), 9.28 (s, 1H), 8.30 (s, 1H), 8.12 (d, 1H, J= 3.6 Hz), 8.00 (m, 1H), 7.49 (d, 1H, J= 7.5 Hz), 7.42 (d, 1H, J= 8.4 Hz), 7.30 (m, 1H), 7.12 (bs, 1H), 7.03 (t, 1H, J= 8.1 Hz), 6.46 (m, 1H), 4.21 (s, 2H), 4.15 (q, 2H, J= 6.9 Hz), 1.19 (t, 3H, J= 7.2 Hz); LCMS: purity: 90%; MS (m/e): 451 (MH<sup>+</sup>).

**7.3.795 N2,N4-Bis(3-boronylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926836)**

A mixture of 2,4-dichloro-5-fluoro-pyrimidine (1 equivalents) and 3-aminophenylboronic acid (3 equivalents) in MeOH was heated in a sealed tube at 100 °C for 24 hours. The resulting mixture was cooled to room temperature, acidified with 2N HCl and the solid obtained was filtered, washed with water, dried and analyzed to give N2,N4-bis(3-boronylphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.40 (s, 1H), 10.07 (s, 1H), 8.25 (d, 8.4 Hz), 7.85 (s, 1H), 7.73 (d, 1H, J= 7.5 Hz), 7.63 (bt, 3H), 7.48 (d, 1H, J= 6.9 Hz), 7.30 (t, 1H, J= 8.4 Hz), 7.12 (t, 1H, J= 2.5 Hz); LCMS: purity: 85%; MS (m/e): 368 (MH<sup>+</sup>).

**7.3.796 N2-(3-Boronylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926837)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 3-aminophenylboronic acid gave N2-(3-boronylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 99%; MS (m/e): 383 (MH<sup>+</sup>).

**7.3.797 (+)-N4-(3,4-Difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R927030)**

A mixture of equivalent amount of 2-chloro-N4-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine and (+)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran in MeOH was shaken in a sealed tube at 80 °C for 48 h, cooled to room temperature and diluted with a mixture of n-hexanes:EtOAc (1:1; v/v). The resulting solid formed was filtered, washed with a mixture of EtOAc:n-hexanes (1:1; v/v), dried and analyzed to give (+)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.21 (bs, 1H), 9.80 (bs, 1H), 8.20 (d, 1H, J= 4.8 Hz), 7.94 (bs, 1H), 7.43 (m, 3H), 7.15 (bd, 1H, J= 8.4 Hz), 6.81 (d, 1H, J= 8.1 Hz), 5.35 (dd, 1H, J= 6.0 and 6.3 Hz), 3.69 (s, 3H), 3.52 (dd, 1H, J= 10.5), 3.22 (dd, 1H, J= 9.0 and 6.0 Hz); LCMS: purity: 99%; MS (m/e): 417 (MH<sup>+</sup>).

**7.3.798 (+)-N4-(4-Chlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R927024)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (+)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine gave (+)-N4-(4-chlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.29 (bs, 1H), 9.89 (bs, 1H), 8.21 (d, 1H, J= 4.8 Hz), 7.69 (m, 2H), 7.38 (m, 3H), 7.13 (bd, 1H, J= 8.1 Hz), 6.83 (d, 1H, J= 8.4 Hz), 5.36 (dd, 1H, J= 6.3 and 5.7 Hz), 3.70 (s, 3H), 3.52 (dd, 1H, J= 10.5 Hz), 3.20 (dd, 1H, J= 5.4 and 5.7 Hz); LCMS: purity: 98%; MS (m/e): 415 (MH<sup>+</sup>).

**7.3.799 (+)-N4-(3,4-Dichlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R927031)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (+)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine gave (+)-N4-(3,4-dichlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):

$\delta$  10.13 (bs, 1H), 9.70 (bs, 1H), 8.21 (d, 1H,  $J$  = 4.8 Hz), 8.04 (d, 1H,  $J$  = 2.4 Hz), 7.68 (m, 1H), 7.54 (d, 1H,  $J$  = 9.0 Hz), 7.37 (bs, 1H), 7.19 (m, 1H), 6.80 (d, 1H,  $J$  = 8.7 Hz), 5.35 (dd, 1H,  $J$  = 6.6 Hz), 3.69 (s, 3H), 3.53 (dd, 1H,  $J$  = 10.5 and 11.1 Hz), 3.21 (dd, 1H,  $J$  = 6.0 Hz); LCMS: purity: 100%; MS ( $m/e$ ): 450 ( $MH^+$ ).

5                      **7.3.800    (+)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-2,4-pyrimidinediamine (R927032)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (+)-5-  
10 amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine gave (+)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-2,4-pyrimidinediamine.  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  10.03 (bs, 2H), 8.18 (d, 1H,  $J$  = 4.8 Hz), 7.68 (bd, 1H,  $J$  = 8.1 Hz), 7.27 (bs, 1H), 6.98 (bd, 1H,  $J$  = 8.1 Hz), 6.69 (d, 1H,  $J$  = 8.7 Hz), 6.44  
15 (d, 1H,  $J$  = 8.1 Hz), 5.33 (dd, 1H,  $J$  = 5.7 Hz), 3.88 (s, 3H), 3.86 (s, 3H), 3.69 (s, 3H), 3.42 (dd, 1H,  $J$  = 10.8 and 11.1 Hz), 3.10 (dd, 1H,  $J$  = 6.3 and 6.6 Hz); LCMS: purity: 99%; MS ( $m/e$ ): 442 ( $MH^+$ ).

20                      **7.3.801    (+)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927025)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (+)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-4-pyrimidineamine gave (+)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-  
25 2,4-pyrimidinediamine.  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  10.10 (bs, 1H), 9.70 (bs, 1H), 8.46 (m, 1H), 8.13 (d, 1H,  $J$  = 4.8 Hz), 7.92 (m, 1H), 7.41 (bs, 1H), 7.12 (bdd, 1H,  $J$  = 8.4 Hz), 6.79 (m, 2H), 5.35 (dd, 1H,  $J$  = 5.7 and 6.0 Hz), 4.24 (t, 2H,  $J$  = 5.1 Hz), 3.70 (s, 3H), 3.69 (t, 2H,  $J$  = 5.1 Hz), 3.52 (dd, 1H,  $J$  = 11.1 Hz), 3.24 (dd, 1H,  $J$  = 6.6 Hz); LCMS: purity: 92%; MS  
30 ( $m/e$ ): 442 ( $MH^+$ ).

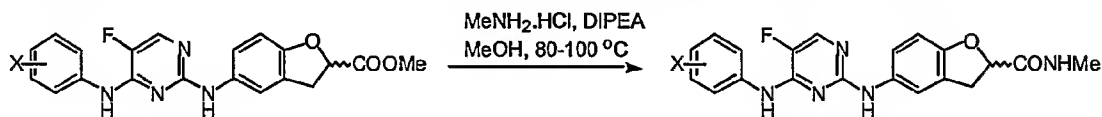
**7.3.802**    **(±)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluorophenyl)-2,4-pyrimidinediamine (R927028)**

In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-5-fluoro-N4-(3-trifluorophenyl)-4-pyrimidineamine gave (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluorophenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.32 (bs, 1H), 9.90 (bs, 1H), 8.23 (d, 1H, J= 4.8 Hz), 7.80 (bd, 1H, J= 6.9 Hz), 7.73 (bs, 1H), 7.43 (t, 1H, J= 8.1 Hz), 7.36 (bs, 1H), 7.16 (m, 2H), 6.79 (d, 1H, J= 8.1 Hz), 5.33 (dd, 1H, J= 6.0 and 6.6 Hz), 3.69 (s, 3H), 3.51 (dd, 1H, J= 10.5 Hz), 3.20 (dd, 1H, J= 6.0 Hz); LCMS: purity: 98%; MS (m/e): 465 (MH<sup>+</sup>).

**7.3.803**    **(±)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927029)**

In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.36 (bs, 1H), 9.93 (bs, 1H), 8.22 (d, 1H, J= 4.8 Hz), 7.91 (bs, 1H), 7.38 (m, 3H), 7.15 9bd, 1H, J= 8.7 Hz), 6.79 (d, 1H, J= 6.0 Hz), 5.33 (dd, 1H, J= 6.3 and 6.6 Hz), 3.69 (s, 3H), 3.50 (dd, 1H, J= 10.5 and 10.8 Hz), 3.22 (dd, 1H, J= 6.0 Hz); LCMS: purity: 100%; MS (m/e): 461 (MH<sup>+</sup>).

25       Esters were transformed to amides allowing to the scheme illustrated below:



**7.3.804**    **(±)-N4-(3,4-Difluorophenyl)-5-fluoro-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R927035)**

30       A mixture of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, methylamine Hydrogen

Chloride (5 equivalents) and diisopropylethylamine (5 equivalents) in MeOH was shaken in a sealed tube at 80 °C for 24 h. The resulting solution was diluted with water and the precipitate obtained was filtered, washed with water, dried and analyzed to afford (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.46 (s, 1H), 9.07 (s, 1H), 8.05 (m, 3H), 7.48 (m, 2H), 7.35 (m, 1H), 7.22 (m, 1H), 6.72 (d, 1H, J= 8.1 Hz), 5.07 (dd, 1H, J= 6.6 and 6.3 Hz), 3.40 (dd, 1H), 3.15 (dd, 1H), 2.60 (d, 3H, J= 4.5 Hz); LCMS: purity: 98%; MS (m/e): 416 (MH<sup>+</sup>).

10                                    **7.3.805    (+)-N4-(4-Chlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927036)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (+)-N4-(4-chlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine gave (+)-N4-(4-chlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.40 (s, 1H), 9.02 (s, 1H), 8.05 (m, 2H), 7.84 (dd, 2H, J= 2.7 and 9.3 Hz), 7.51 (bs, 1H), 7.32 (bd, 2H, J= 8.7 Hz), 7.23 (bd, 1H, J= 8.7 Hz), 6.72 (d, 1H, J= 8.7 Hz), 5.07 (dd, 1H, J= 6.0 and 6.3 Hz), 3.39 (dd, 1H), 3.17 (dd, 1H), 2.60 (d, 3H, J= 4.8 Hz); LCMS: purity: 99%; MS (m/e): 414 (MH<sup>+</sup>).

20                                    **7.3.806    (+)-N4-(3,4-Dichlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927037)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (+)-N4-(3,4-dichlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine gave (+)-N4-(3,4-dichlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.52 (s, 1H), 9.09 (s, 1H), 8.08 (m, 3H), 7.76 (bd, 1H, J= 9.3 Hz), 7.50 (d, 1H, J= 9.0 Hz), 7.43 (bs, 1H), 7.24 (bd, 1H, J= 8.7 Hz), 6.73 (d, 1H, J= 8.1 Hz), 5.07 (dd, 1H, J= 6.3 and 6.6 Hz), 3.39 (dd, 1H, J= 10.5 Hz), 3.15 (dd, 1H, J= 6.3 Hz), 2.60 (d, 3H, J= 4.8 Hz); LCMS: purity: 99%; MS (m/e): 450 (MH<sup>+</sup>).



**7.3.807 (+)-N4-(2,6-Dimethoxypyridin-3-yl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927038)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (+)-N4-(2,6-dimethoxypyridin-3-yl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine gave (+)-N4-(2,6-dimethoxypyridin-3-yl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.98 (d, 1H, J= 8.1 Hz), 7.81 (d, 1H, J= 3.6 Hz), 7.39 (bd, 1H, J= 2.4 Hz), 7.06 (dd, 1H, J= 2.4 and 8.7 Hz), 6.72 (d, 1H, J= 8.1 Hz), 6.31 (d, 1H, J= 8.7 Hz), 5.07 (dd, 1H, J= 6.3 Hz), 3.96 (s, 3H), 3.93 (s, 3H), 3.46 (dd, 1H, J= 7.8 and 10.5 Hz), 3.19 (dd, 1H, J= 5.7 and 6.3 Hz), 2.77 (d, 3H, J= 4.8 Hz); LCMS: purity: 98%; MS (m/e): 441 (MH<sup>+</sup>).

**7.3.808 (+)-N2-[2,3-Dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-2,4-pyrimidinediamine (R927039)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (+)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-2,4-pyrimidinediamine gave (+)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.26 (s, 1H), 8.99 (s, 1H), 8.50 (bd, 1H, J= 3.0 Hz), 8.02 (bd, 2H, J= 3.6 Hz), 7.94 (dd, 2H, J= 2.7 and 5.1 Hz), 7.52 (bs, 1H), 7.20 (bd, 1H, J= 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.67 (d, 1H, J= 8.7 Hz), 5.05 (dd, 1H, J= 6.3 and 6.6 Hz), 4.80 (t, 1H), 4.23 (t, 2H, J= 5.1 Hz), 3.69 (q, 2H, J= 5.4 Hz), 3.40 (dd, 1H), 3.15 (dd, 1H, J= 6.3 and 9.9 Hz), 2.60 (d, 3H, J= 4.5 Hz); LCMS: purity: 86%; MS (m/e): 441 (MH<sup>+</sup>).

**7.3.809 (+)-N2-[2,3-Dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R927040)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (+)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine gave (+)-N2-[2,3-

dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. LCMS: purity: 94%; MS (m/e): 464 (MH<sup>+</sup>).

5                                    **7.3.810    (±)-N2-[2,3-Dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-N4-(3,4-difluoromethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927041)**

In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine gave (±)-N2-[2,3-dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-N4-(3,4-difluoromethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.46 (s, 1H), 9.05 (s, 1H), 8.05 (m, 3H), 7.43 (m, 2H), 7.31 (d, 1H, J = 8.7 Hz), 7.23 (bd, 1H, J = 7.5 Hz), 6.70 (d, 1H, J = 9.0 Hz), 5.04 (dd, 1H, J = 6.6 Hz), 3.40 (dd, 1H), 3.14 (dd, 1H, J = 5.7 and 6.6 Hz), 2.60 (d, 3H, J = 3.9 Hz); LCMS: purity: 94%; MS (m/e): 460 (MH<sup>+</sup>).

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**7.3.811    N2-(4-Carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926238)**

The reaction of N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine with LiOH in THF:H<sub>2</sub>O at room temperature gave N2-(carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.16 (d, 1H, J = 4.8 Hz), 7.37 (bd, 2H, J = 9 Hz), 7.25 (d, 1H, J = 3 Hz), 7.08 (m, 1H), 6.83 (m, 3H), 4.64 (s, 2H), 4.23 (s, 4H); LCMS: ret. time: 19.15 min.; purity: 100%; MS (m/e): 413 (MH<sup>+</sup>).

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25                                    **7.3.812    N4-(1,4-Benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R920395)**

To a solution of N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (1 equivalent) in MeOH at 0 °C was added HCl (4M, dioxane, 1.1 equivalents) dropwise and shaken for 5 minutes. The resulting solution was diluted with EtOAc and the solid obtained was filtered washed with EtOAc, dried and analyzed to give N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride

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Salt. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.80 (bs, 2H), 8.12 (d, 1H, J= 4.8 Hz), 7.89 (bd, 1H, J= 4.5 Hz), 7.18 (m, 3H), 8.24 (m, 2H), 6.60 (bd, 2H, J= 8.1 Hz), 4.36 (s, 2H), 4.10 (t, 2H, J= 3.9 Hz), 3.27 (t, 2H, J= 3.9 Hz), 2.62 (d, 3H, J= 4.5 Hz); LCMS: purity: 98%, MS (m/e): 425 (MH<sup>+</sup>).

5                                    **7.3.813    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Trifluoro Acetic Acid Salt (R926826)**

In like manner to the synthesis of N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride  
10 Salt the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine with trifluoroacetic acid gave N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Trifluoro Acetic Acid  
15 Salt. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.40 (bs, 1H), 9.36 (bs, 1H), 8.07 (d, 1H, J= 4.2 Hz), 7.94 (bd, 1H), 7.22 (m, 4H), 7.11 (t, 1H, J= 7.5 Hz), 6.79 (d, 1H, J= 8.7 Hz), 6.51 (bd, 1H, J= 7.5 Hz), 4.33 (s, 2H), 4.21 (bs, 4H), 2.63 (d, 3H, 3.3 Hz).

20                                    **7.3.814    5-Fluoro-N4-[(1H)-indol-6-yl]-N2-[4-methoxy-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926752)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 4-methoxy-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-[(1H)-indol-6-yl]-N2-[4-methoxy-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ  
25 7.83 (d, 1H, J= 3.6 Hz), 7.73 (d, 1H, J= 0.9 Hz), 7.49 (d, 1H, J= 8.1 Hz), 7.39 (d, 1H, J= 3.0 Hz), 7.20 (d, 1H, J= 3.6 Hz), 7.15 (dd, 1H, J= 1.8 and 8.1 Hz), 7.05 (dd, 1H, J=2.1 and 8.7 Hz), 6.81 (d, 1H, J= 8.7 Hz), 6.41 (d, 1H, J= 4.2 Hz), 4.09 (s, 2H), 3.81 (s, 3H), 2.76 (s, 3H); LCMS: purity: 100%; MS (m/e): 437(MH<sup>+</sup>).

**7.3.815 5-Fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926753)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy] aniline were reacted to produce 5-fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.95 (bs, 1H), 9.83 (bs, 1H), 9.38 (bs, 1H), 8.17 (d, 1H, J= 4.4 Hz), 7.97 (d, 1H, J= 4.8 Hz), 7.24-7.17 (m, 2H), 7.16 (d, 1H, J= 8.4 Hz), 7.10 (dd, 1H, J=1.8 and 8.4 Hz), 7.03 (d, 1H, J= 2.4 Hz), 7.00 (d, 1H, J= 9.0 Hz), 6.61 (d, 1H, J= 8.7 Hz), 4.34 (s, 2H), 2.63 (d, 3H, J= 4.5 Hz), 2.08 (s, 3H); LCMS: purity: 96%; MS (m/e): 398(MH<sup>+</sup>).

**7.3.816 5-Fluoro-N4-(3-dihydroxyborylphenyl)- N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926754)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-dihydroxyborylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-dihydroxyborylphenyl)- N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.38 (bs, 1H), 9.22 (bs, 1H), 8.08 (d, 1H, J= 3.6 Hz), 8.06-7.81 (m, 4H), 7.51 (d, 1H, J= 8.1 Hz), 7.33-7.28 (m, 3H), 7.06 (t, 1H, J= 8.1 Hz), 6.44 (dd, 1H, J= 2.4 and 7.5 Hz), 4.33 (s, 2H), 2.63 (d, 3H, J= 4.8 Hz); LCMS: purity: 95%; MS (m/e): 412(MH<sup>+</sup>).

**7.3.817 5-Fluoro-N4-(3-dihydroxyborylphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926755)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-dihydroxyborylphenyl)-4-pyrimidineamine and 3-hydroxyaniline were reacted to produce 5-Fluoro-N4-(3-dihydroxyborylphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.68 (bs, 1H), 9.35 (bs, 1H), 9.22 (bs, 1H), 8.10 (d, 1H, J= 3.9 Hz), 7.88-7.80 (m, 2H), 7.54 (d, 1H, J= 7.2 Hz), 7.31 (t, 1H, J= 7.2 Hz), 7.08 (d, 1H, J= 8.4 Hz), 6.98-6.93 (m, 2H), 6.35 (d, 1H, J= 8.4 Hz); LCMS: purity: 96%; MS (m/e): 341(MH<sup>+</sup>).

**7.3.818 N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxyborylphenyl)-2,4-pyrimidinediamine (R926756)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-dihydroxyborylphenyl)-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to produce N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxyborylphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.46 (bs, 1H), 9.11 (bs, 1H), 8.05 (d, 1H, J= 4.2 Hz), 7.95 (bs, 1H), 7.88 (s, 1H), 7.78 (d, 1H, J= 7.5 Hz), 7.52 (d, 1H, J= 7.5 Hz), 7.29 (t, 1H, J= 7.5 Hz), 7.16 (s, 1H), 7.02 (d, 1H, J= 8.7 Hz), 6.65 (d, 1H, J= 8.7 Hz), 3.40 (s, 4H); LCMS: purity: 98%; MS (m/e): 383(MH<sup>+</sup>).

**7.3.819 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926757)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.32 (s, 1H), 9.17 (s, 1H), 9.04 (s, 1H), 8.04 (d, 1H, J= 4.2 Hz), 7.76 (d, 1H, J= 4.8 Hz), 7.32 (td, 2H, J= 1.8 and 8.1 Hz), 7.13-7.04 (m, 3H), 6.95 (d, 1H, J= 8.4 Hz), 6.46 (dd, 1H, J= 1.8 and 8.4 Hz), 4.31 (s, 2H), 2.65 (d, 3H, J= 4.8 Hz), 2.14 (s, 3H); LCMS: purity: 99%; MS (m/e): 398(MH<sup>+</sup>).

**7.3.820 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro- N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926758)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro- N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.13 (bs, 1H), 9.05 (s, 1H), 8.01 (d, 1H, J= 4.2 Hz), 7.76 (d, 1H, J= 4.8 Hz), 7.32 (d, 1H, J= 2.4 Hz), 7.27 (dd, 1H, J= 2.4 and 8.1 Hz), 7.21 (dd, 1H, J= 2.4 and 8.7 Hz), 7.13 (d,

1H, J= 1.8 Hz), 6.95 (d, 1H, J= 8.1 Hz), 6.76 (d, 1H, J= 8.7 Hz), 4.28 (s, 2H), 4.20 (s, 4H), 2.65 (d, 3H, J= 4.8 Hz), 2.15 (s, 3H); LCMS: purity: 97%; MS (m/e): 440(MH<sup>+</sup>).

5                    **7.3.821    5-Fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926759)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.09 (bs, 1H), 9.96 (bs, 1H), 9.44 (bs, 1H), 8.16 (d, 1H, J= 4.8 Hz), 7.81 (d, 1H, J= 4.8 Hz), 7.13-6.94 (m, 6H), 4.29 (s, 2H), 2.64 (d, 3H, J= 4.5 Hz), 2.17 (s, 3H), 2.07 (s, 3H); LCMS: purity: 99%; MS (m/e): 412(MH<sup>+</sup>).

15                    **7.3.822    5-Fluoro-N2,N4-bis[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926760)**

In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2,N4-bis[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.30 (s, 1H), 9.02 (s, 1H), 8.06 (d, 1H, J= 3.6 Hz), 7.94 (d, 1H, J= 4.5 Hz), 7.80 (d, 1H, J= 4.2 Hz), 7.58 (bs, 1H), 7.31-7.22 (m, 3H), 7.05 (d, 1H, J= 9.0 Hz), 6.97 (d, 1H, J= 7.5 Hz), 4.41 (s, 2H), 4.27 (s, 2H), 2.66 (d, 3H, J= 4.2 Hz), 2.63 (d, 3H, J= 4.2 Hz), 2.18 (s, 3H), 2.14 (s, 3H); LCMS: purity: 100%; MS (m/e): 483(MH<sup>+</sup>).

**7.3.823    5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (R926761)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3,4,5-trimethoxyaniline were reacted to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.33 (s, 1H), 9.17 (s, 1H), 8.99 (s, 1H), 8.06 (d, 1H, J= 3.3 Hz), 7.27 (d, 1H, J= 7.5

Hz), 7.08-7.02 (m, 4H), 6.46 (dd, 1H, J= 1.8 and 7.8 Hz), 3.60 (s, 6H), 3.57 (s, 3H); LCMS: purity: 99%; MS (m/e): 387(MH<sup>+</sup>).

**7.3.824 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (R926762)**

5 In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,4,5-trimethoxyaniline were reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine  
10 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.08 (d, 1H, J= 4.8 Hz), 7.29 (d, 1H, J= 2.4 Hz), 7.15 (dd, 1H, J=3.0 and 9.0 Hz), 6.91 (s, 1H), 6.76 (d, 1H, J= 8.7 Hz), 4.20 (s, 4H), 3.61 (s, 6H), 3.59 (s, 3H); LCMS: purity: 97%; MS (m/e): 429(MH<sup>+</sup>).

**7.3.825 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-2,4-pyrimidinediamine (R926763)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-  
15 (3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,5-dichloro-4-hydroxyaniline were reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.50 (bs, 1H), 9.26 (bd, 2H, J= 7.5 Hz), 8.06 (d, 1H, J= 3.9 Hz), 7.65 (s, 2H), 7.18-7.13 (m, 2H), 6.80 (d, 1H, J= 9.0 Hz), 4.20 (s, 4H);  
20 LCMS: purity: 100%; MS (m/e): 424(MH<sup>+</sup>).

**7.3.826 5-Fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926890)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-  
25 pyrimidineamine and 3,5-dichloro-4-hydroxyaniline were reacted to produce 5-Fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.47 (bs, 1H), 9.35 (bs, 1H), 9.22 (bs, 2H), 8.09 (d, 1H, J= 3.6 Hz), 7.70 (s, 2H), 7.31 (dd, 1H, J= 1.2 and 9.3 Hz), 7.10 (t, 1H, J= 7.5 Hz), 7.00 (bs, 1H), 6.48 (dd, 1H, J= 1.2 and 6.9 Hz); LCMS: purity: 93%; MS (m/e): 382(MH<sup>+</sup>).

**7.3.827 N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926891)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.85 (bs, 1H), 9.70 (bs, 1H), 8.17 (d, 1H, J= 4.8 Hz), 7.98 (d, 1H, J= 3.9 Hz), 7.79 (d, 1H, J= 2.4 Hz), 7.65 (dd, 1H, J= 3.0 and 9.3 Hz), 7.24-7.09 (m, 4H), 6.57 (d, 1H, J= 5.7 Hz), 4.34 (s, 2H), 3.82 (s, 3H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 95%; MS (m/e): 433(MH<sup>+</sup>).

**7.3.828 5-Fluoro-N4-(3-fluoro-4-methoxyphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926892)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-fluoro-4-methoxyphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-fluoro-4-methoxyphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.68 (bs, 1H), 9.53 (bs, 1H), 8.13 (d, 1H, J= 4.2 Hz), 7.97 (d, 1H, J= 4.8 Hz), 7.76 (dd, 1H, J= 2.4 and 13.5 Hz), 7.47 (d, 1H, J= 7.5 Hz), 7.27-7.08 (m, 4H), 6.54 (d, 1H, J= 8.4 Hz), 4.35 (s, 2H), 3.80 (s, 3H), 2.63 (d, 3H, J= 4.8 Hz); LCMS: purity: 94%; MS (m/e): 416(MH<sup>+</sup>).

**7.3.829 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxy-5-methylphenyl)-2,4-pyrimidinediamine (R926893)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 4-amino-*m*-cresol hydrogenschloride salt, and diisopropylethylamine were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxy-5-methylphenyl)-2,4-pyrimidinediamine.



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.06 (s, 1H), 8.94 (s, 1H), 8.11 (s, 1H), 7.86 (d, 1H, J= 3.9 Hz), 7.21-7.15 (m, 2H), 7.03 (d, 1H, J= 8.1 Hz), 6.59 (bd, 2H, J= 8.7 Hz), 6.52 (dd, 1H, J= 3.0 and 8.1 Hz), 4.17 (s, 4H), 2.05 (s, 3H); LCMS: purity: 99%; MS (m/e): 369(MH<sup>+</sup>).

5                    **7.3.830    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-fluoro-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926894)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-amino-5-fluorobenzotrifluoride were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-fluoro-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.75 (s, 1H), 9.32 (d, 1H, J= 1.2 Hz), 8.13 (d, 1H, J= 3.6 Hz), 7.99 (d, 1H, J= 12.3 Hz), 7.77 (s, 1H), 7.21 (d, 1H, J= 2.4 Hz), 7.13 (dd, 1H, J= 2.1 and 8.7 Hz), 7.03 (d, 1H, J= 9.0 Hz), 6.80 (d, 1H, J= 8.7 Hz), 4.21 (s, 4H); LCMS: purity: 97%; MS (m/e): 425(MH<sup>+</sup>).

15                    **7.3.831    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-methyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926895)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-amino-5-methylbenzotrifluoride were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.57 (bs, 1H), 9.39 (bs, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.77 (s, 2H), 7.25-7.13 (m, 2H), 7.02 (s, 1H), 6.79 (d, 1H, J= 9.0 Hz), 4.20 (s, 4H), 2.27 (s, 3H); LCMS: purity: 100%; MS (m/e): 421(MH<sup>+</sup>).

25                    **7.3.832    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(5-methoxy-2-methylphenyl)-2,4-pyrimidinediamine (R926896)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 5-methoxy-2-methylaniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(5-methoxy-2-methylphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.91 (bs, 1H), 7.61 (d, 1H, J= 2.1 Hz), 7.17 (d, 1H, J= 3.0 Hz), 7.05 (d, 1H, J= 9.3 Hz), 7.03 (dd, 1H, J= 3.0 and 8.7 Hz),

6.82 (d, 1H, J= 8.1 Hz), 6.68-6.60 (m, 2H), 6.55 (dd, 1H, J= 2.1 and 8.1 Hz), 4.26 (s, 4H), 3.70 (s, 3H), 2.22 (s, 3H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ): -47450; LCMS: purity: 99%; MS (m/e): 383( $\text{MH}^+$ ).

5                                    **7.3.833    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-fluoro-5-methylphenyl)-2,4-pyrimidinediamine (R926897)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2-fluoro-5-methylaniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-fluoro-5-methylphenyl)-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.11 (dd, 1H, J= 1.8 and 8.1 Hz), 7.94 (d, 1H, J= 2.7 Hz), 7.08-6.84 (m, 4H), 6.74-6.67 (m, 1H), 6.64-6.59 (m, 1H), 4.27 (s, 4H), 2.28 (s, 3H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ): -38659, -47267; LCMS: purity: 100%; MS (m/e): 371( $\text{MH}^+$ ).

15                                    **7.3.834    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3,5-difluorophenyl)-2,4-pyrimidinediamine (R926898)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,5-difluoroaniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3,5-difluorophenyl)-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.94 (d, 1H, J= 3.3 Hz), 7.20-7.11 (m, 3H), 7.02 (s, 1H), 6.92-6.90 (m, 2H), 6.65 (s, 1H), 6.39 (tt, 1H, J= 2.4 and 9.0 Hz), 4.31 (s, 4H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ): -31142, -47002; LCMS: purity: 97%; MS (m/e): 375( $\text{MH}^+$ ).

25                                    **7.3.835    N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-trifluoromethylthiophenyl)-2,4-pyrimidinediamine (R926899)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-(trifluoromethylthio)aniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-trifluoromethylthiophenyl)-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  9.73 (s, 1H), 9.47 (s, 1H), 8.13 (d, 1H, J= 3.6 Hz), 7.79 (d, 2H, J= 9.0 Hz), 7.51 (d, 2H, J= 9.0 Hz), 7.28

(d, 1H, J= 2.1 Hz), 7.12 (dd, 1H, J= 2.4 and 9.0 Hz), 6.83 (d, 1H, J= 8.7 Hz), 4.23 (s, 4H);  
<sup>19</sup>F NMR (282 MHz DMSO-*d*<sub>6</sub>): -12306; LCMS: purity: 97%; MS (m/e): 439(MH<sup>+</sup>).

5                    **7.3.836    N4-[3-(Benzothiazol-2-yl)-4-chlorophenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926900)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[3-(Benzothiazol-2-yl)-4-chlorophenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide N4-[3-(benzothiazol-2-yl)-4-chlorophenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.77 (s, 1H), 9.30 (s, 1H), 8.49 (d, 1H, J= 3.0 Hz), 8.25 (dd, 1H, J= 3.0 and 9.0), 8.21-8.16 (m, 2H), 8.06 (d, 1H, J= 7.8 Hz), 7.92 (d, 1H, J= 4.8 Hz), 7.63-7.48 (m, 3H), 7.30 (t, 1H, J= 1.8 Hz), 7.22 (dd, 1H, J= 1.8 and 7.5 Hz), 6.95 (t, 1H, J= 8.1 Hz), 6.32 (dd, 1H, J= 1.2 and 8.1 Hz), 4.29 (s, 2H), 2.62 (d, 1H, J= 4.8 Hz); LCMS: purity: 100%; MS (m/e): 536(MH<sup>+</sup>).

20                    **7.3.837    5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-methoxy-4-methylphenyl)-2,4-pyrimidinediamine (R926902)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-Chloro-5-fluoro-N4-(3-methoxy-4-methylphenyl)-4-pyrimidineamine and 3-methoxy-4-methylaniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-methoxy-4-methylphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.78 (bs, 1H), 9.63 (bs, 1H), 8.15 (d, 1H, J= 4.5 Hz), 7.94 (d, 1H, J= 4.5 Hz), 7.94 (d, 1H, J= 4.5 Hz), 7.30 (dd, 1H, J= 1.8 and 8.4 Hz), 7.25-7.04 (m, 5H), 6.57 (d, 1H, J= 8.1 Hz), 4.31 (s, 2H), 3.66 (s, 3H), 2.62 (d, 1H, J= 4.8 Hz), 2.09 (s, 3H); LCMS: purity: 95%; MS (m/e): 412(MH<sup>+</sup>).

30                    **7.3.838    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926903)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 6-amino-2-(methoxycarbonyl)-(1H)-

indole were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.53 (s, 1H), 9.37 (s, 1H), 9.18 (d, 2H, J= 9.9 Hz), 8.08 (d, 1H, J= 3.6 Hz), 7.96 (bs, 1H), 7.46 (d, 1H, J= 9.0 Hz), 7.39-7.35 (m, 2H), 7.16 (t, 1H, J= 2.4 Hz), 7.10-7.04 (m, 2H), 6.48 (dd, 1H, J= 2.4 and 7.5 Hz), 3.82 (s, 3H); LCMS: purity: 95%; MS (m/e): 394(MH<sup>+</sup>).

**7.3.839 5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926904)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.05 (bs, 1H), 8.35 (s, 1H), 8.00 (bs, 1H), 7.66-7.62 (m, 2H), 7.27-7.17 (m, 3H), 7.01-6.90 (m, 3H), 6.64 (dd, 1H, J= 2.4 and 8.1 Hz), 6.40 (bs, 1H), 4.49 (s, 2H), 3.94 (s, 3H), 2.75 (d, 3H, J= 5.1 Hz); LCMS: purity: 86%; MS (m/e): 465(MH<sup>+</sup>).

**7.3.840 N4-[3-[[4-(Ethoxycarbonyl)piperidino]methyl]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926905)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[3-[[4-(ethoxycarbonyl)piperidino]methyl]phenyl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-[3-[[4-(ethoxycarbonyl)piperidino]methyl]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 9.33 (s, 1H), 9.20 (s, 1H), 8.09 (d, 1H, J= 4.2 Hz), 7.93 (d, 1H, J= 4.8 Hz), 7.82 (d, 1H, J= 8.1 Hz), 7.55 (s, 1H), 7.35 (t, 1H, J= 2.4 Hz), 7.29-7.22 (m, 2H), 7.09 (t, 1H, J= 8.1 Hz), 6.96 (d, 1H, J= 7.8 Hz), 6.47 (dd, 1H, J= 2.4 and 8.1 Hz), 4.32 (s, 2H), 4.02 (q, 2H, J= 6.9 Hz), 3.39 (s, 2H), 2.73 (bd, 2H, J=11.1 Hz), 2.63 (d, 3H, J= 4.5 Hz), 2.30-2.20 (m, 1H),

1.94 (t, 2H, J= 11.1 Hz), 1.74 (d, 2H, J= 9.9 Hz), 1.60-1.50 (m, 2H), 1.14 (t, 3H, J= 6.9 Hz); LCMS: purity: 99%; MS (m/e): 537(M - CH<sub>2</sub><sup>+</sup>).

5                   **7.3.841    N2-[3-(Ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926906)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)aniline were reacted to provide N2-[3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.91 (d, 1H, J= 4.8 Hz), 7.20-7.03 (m, 6H), 6.67 (td, 1H, J= 2.1 and 7.5 Hz), 6.57-6.53 (m, 1H), 4.19 (q, 2H, J= 6.9 Hz), 1.53 (s, 6H), 1.20 (t, 3H, J= 6.9 Hz); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -46120; LCMS: purity: 91%; MS (m/e): 427(MH<sup>+</sup>).

15                   **7.3.842    N2-[3-(Ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926907)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)aniline were reacted to provide N2-[3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.92 (d, 1H, J= 3.0 Hz), 7.21-7.08 (m, 4H), 7.00 (dd, 1H, J= 2.4 and 8.4 Hz), 6.93 (bs, 1H), 6.86 (d, 1H, J= 8.7 Hz), 6.99 (d, 1H, J= 2.4 Hz), 6.45 (ddd, 1H, J= 1.2, 1.2, and 7.8 Hz), 4.27 (s, 4H), 4.23 (q, 2H, J= 6.9 Hz), 1.60 (s, 6H), 1.23 (t, 3H, J= 6.9 Hz); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): -47216; LCMS: purity: 85%; MS (m/e): 469(MH<sup>+</sup>).

30                   **7.3.843    N2-[3-(Ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxy-4-methylphenyl)-2,4-pyrimidinediamine (R926908)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)aniline were reacted to provide N2-[3-(ethoxycarbonyl-1,1-

dimethylmethylenedioxyphenyl]-5-fluoro-N4-(3-hydroxy-4-methylphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.86 (bs, 1H), 7.80 (bs, 1H), 7.53 (s, 1H), 7.16-6.86 (m, 4H), 6.54 (d, 2H, J= 7.5 Hz), 4.21 (q, 2H, J= 6.9 Hz), 3.48 (s, 2H), 2.20 (s, 3H), 1.60 (s, 6H), 1.22 (t, 3H, J= 6.9 Hz); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): -46808; LCMS: purity: 96%; MS (m/e): 441(MH<sup>+</sup>).

**7.3.844 N2-[3-(Ethoxycarbonyl-1,1-dimethylmethylenedioxy)phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926909)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methylenedioxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethylenedioxy)aniline were reacted to provide N2-[3-(Ethoxycarbonyl-1,1-dimethylmethylenedioxy)phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.43 (bs, 1H), 8.64 (s, 1H), 7.92 (d, 1H, J= 3.6 Hz), 7.66 (t, 1H, J= 2.4 Hz), 7.54 (d, 1H, J= 8.4 Hz), 7.44 (s, 1H), 7.19 (t, 1H, J= 3.0 Hz), 7.15 (d, 1H, J= 8.1 Hz), 6.96 (d, 1H, J= 3.0 Hz), 6.80 (dd, 1H, J= 1.8 and 7.5 Hz), 6.77 (dd, 1H, J= 1.8 and 8.1 Hz), 6.52 (dd, 1H, J= 1.8 and 7.5 Hz), 6.49-6.46 (m, 1H), 4.32 (q, 2H, J= 7.2 Hz), 1.57 (s, 6H), 1.31 (t, 3H, J= 7.2 Hz); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): -47190; LCMS: purity: 93%; MS (m/e): 450(MH<sup>+</sup>).

**7.3.845 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethylenedioxy]phenyl]-2,4-pyrimidinediamine (R926913)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methylenedioxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(N-methylamino)carbonyl-1,1-dimethylmethylenedioxyaniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethylenedioxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.35 (s, 1H), 9.20 (s, 1H), 9.17 (s, 1H), 8.07 (d, 1H, J= 3.3 Hz), 7.93 (d, 1H, J= 3.9 Hz), 7.40-7.29 (m, 3H), 7.13-7.02 (m, 3H), 6.47 (d, 1H, J= 7.5 Hz), 6.33 (d, 1H, J= 7.5 Hz), 2.60 (s, 3H), 1.37 (s, 6H); LCMS: purity: 97%; MS (m/e): 412(MH<sup>+</sup>).

**7.3.846 5-Fluoro-N4-(1,2,3,4-tetrahydroisoquin-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926914)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-(1,2,3,4-tetrahydroisoquin-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.90 (d, 1H, J= 3.3 Hz), 7.47 (d, 1H, J= 2.4 Hz), 7.42-7.37 (m, 2H), 7.16 (t, 1H, J= 8.4 Hz), 7.10-7.04 (m, 2H), 6.50 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 4.26 (s, 2H), 3.93 (s, 2H), 3.12 (t, 2H, J= 6.3 Hz), 2.84-2.76 (m, 5H), ; <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -47489; LCMS: purity: 87%; MS (m/e): 423(MH<sup>+</sup>).

**7.3.847 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro- N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926915)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-(N-methylamino)carbonyl-1,1-dimethylmethyleneoxyaniline were reacted to provide N4-(3,4-Ethylenedioxyphenyl)-5-fluoro- N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.26 (t, 1H, J= 7.5 Hz), 7.19 (d, 1H, J= 9.3 Hz), 7.13 (d, 1H, J= 2.4 Hz), 7.06 (dd, 1H, J= 2.4 and 8.7 Hz), 7.04-7.03 (m, 1H), 6.83 (d, 1H, J= 9.0 Hz), 6.75 (d, 1H, J= 7.2 Hz), 4.25 (s, 4H), 2.76 (s, 3H), 1.43 (s, 6H); LCMS: purity: 97%; MS (m/e): 454(MH<sup>+</sup>).

**7.3.848 5-Fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine (R926917)**

A mixture of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (20 mg, 0.052 mmol), allyl isocyanate (13mg, 0.16 mmol), and 2-(N,N-dimethylamino)pyridine (18 mg, 0.15 mmol) in anhydrous THF (1 mL) were heated at 60°C in a sealed vial for 2 days. The reaction was diluted with ethyl acetate and washed with 1N HCl and brine. Concentration gave an oily residue which was

purified by preparative TLC (5% methanol/dichloromethane) to give the product 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.93 (d, 1H, J= 3.6 Hz), 7.62-7.55 (m, 2H), 7.32 (s, 1H), 7.30 (t, 1H, J= 8.1 Hz), 7.19-7.15 (m, 2H), 6.82 (dd, 1H, J= 2.4 and 8.1 Hz), 6.61 (m, 1H), 5.96-5.82 (m, 1H), 5.24 (dd, 1H, J= 1.8 and 16.8 Hz), 5.13 (dd, 1H, J= 1.8 and 11.7 Hz), 4.41 (s, 2H), 3.79 (d, 1H, J= 5.4 Hz), 2.80 (s, 3H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -47357; LCMS: purity: 99%; MS (m/e): 468(MH<sup>+</sup>).

**7.3.849 5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[3-[(N-isopropylamino)carbonyl]-N-isopropylamino)carbonyloxy]phenyl]-2,4-pyrimidinediamine (R926916)**

In a like manner to the preparation of 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine and isopropyl isocyanate were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[3-[(N-isopropylamino)carbonyl]-N-isopropylamino)carbonyloxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.40 (bs, 1H), 9.27 (bs, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.94 (d, 1H, J= 3.9 Hz), 7.78 (d, 1H, J= 8.7 Hz), 7.64 (d, 1H, J= 7.5 Hz), 7.46 (s, 1H), 7.36-7.26 (m, 3H), 7.12 (t, 1H, J= 8.1 Hz), 6.81-6.74 (m, 1H), 6.47 (dd, 1H, J= 2.4 and 8.1 Hz), 5.43 (d, 1H, J= 3.9 Hz), 4.36 (s, 2H), 3.65-3.55 (m, 2H), 3.14 (s, 2H), 2.63 (d, 3H, J= 3.9 Hz), 1.10 (d, 6H, J= 7.2 Hz), 0.97 (d, 6H, J= 6.6 Hz).

**7.3.850 N4-[3-[(N-(Ethoxycarbonylmethyl)amino)carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926918)**

In a like manner to the preparation of 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine and ethyl isocyanatoacetate were reacted to provide N4-[3-[(N-(ethoxycarbonylmethyl)amino)carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.94 (d, 1H, J= 3.3 Hz), 7.69 (t, 1H, J= 1.8 Hz), 7.56 (ddd, 1H, J= 1.2, 1.2, and 8.1 Hz), 7.35 (m, 1H), 7.31 (t, 1H, J= 8.1 Hz), 7.18 (d, 1H, J= 2.4 Hz), 7.17 (d, 1H, J= 1.2 Hz), 6.84 (dd, 1H, J= 2.4 and 8.1 Hz), 6.63-6.58 (m, 1H), 4.42 (s, 2H), 4.20 (q, 2H, J= 7.2 Hz), 3.93



(s, 2H), 2.80 (s, 3H), 1.27 (t, 3H, J= 7.2 Hz);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CD}_3\text{OD}$ ): -47371; LCMS: purity: 89%; MS (m/e): 513( $\text{MH}^+$ ).

5                    **7.3.851    N4-[3-[(N-(Ethylamino)carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926919)**

In a like manner to the preparation of 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine and ethyl isocyanate were reacted to provide N4-[3-[(N-(ethylamino)carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.94 (d, 1H, J= 3.3 Hz), 6.84-6.79 (m, 2H), 7.61-7.55 (m, 2H), 6.62-6.56 (m, 2H), 7.33-7.27 (m, 1H), 7.19-7.17 (m, 1H), 4.41 (s, 2H), 3.23 (q, 2H, J= 7.2 Hz), 2.80 (s, 3H), 1.17 (t, 3H, J= 7.2 Hz);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CD}_3\text{OD}$ ): -47378; LCMS: purity: 100%; MS (m/e): 455( $\text{MH}^+$ ).

15                    **7.3.852    5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(4-methyl-3-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926922)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-methyl-3-trifluoromethylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(4-methyl-3-trifluoromethylphenyl)-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  9.79 (bs, 1H), 9.48 (bs, 1H), 8.17 (d, 1H, J= 4.2 Hz), 8.10 (d, 1H, J= 6.3 Hz), 7.96 (d, 1H, J= 4.8 Hz), 7.89 (d, 1H, J= 2.1 Hz), 7.38 (d, 1H, J= 9.0 Hz), 7.26-7.20 (m, 2H), 7.11 (t, 1H, J= 8.4 Hz), 6.53 (d, 1H, J= 8.4 Hz), 4.33 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz), 2.39 (s, 3H); LCMS: purity: 94%; MS (m/e): 450( $\text{MH}^+$ ).

30                    **7.3.853    5-Fluoro-N4-(4-fluoro-3-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926923)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-fluoro-3-methylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-Fluoro-N4-(4-

fluoro-3-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.67 (bs, 1H), 9.51 (bs, 1H), 8.14 (d, 1H, J= 4.8 Hz), 7.95 (d, 1H, J= 4.2 Hz), 7.64 (dd, 1H, J= 2.7 and 6.9 Hz), 7.57-7.50 (m, 1H), 7.23-7.06 (m, 4H), 6.55 (d, 1H, J= 7.5 Hz), 4.33 (s, 2H), 2.63 (d, 3H, J= 4.8 Hz), 2.19 (s, 3H);

5 LCMS: purity: 94%; MS (m/e): 400(MH<sup>+</sup>).

**7.3.854 5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-trifluoromethylthiophenyl)-2,4-pyrimidinediamine (R926925)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-trifluoromethylthiophenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-trifluoromethylthiophenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.83 (bs, 1H), 9.49 (bs, 1H), 8.21-8.15 (m, 2H), 8.01 (s, 1H), 7.94 (bs, 1H), 7.49 (t, 1H, J= 7.8 Hz), 7.38 (d, 1H, J= 7.8 Hz), 7.29 (s, 1H), 7.22 (d, 1H, J= 7.5 Hz), 7.14 (t, 1H, J= 8.4 Hz), 6.54 (d, 1H, J= 9.9 Hz), 4.34 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 98%; MS (m/e): 468(MH<sup>+</sup>).

**7.3.855 N2-[3,5-Bis(methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926926)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3,5-bis(methoxycarbonylmethyleneoxy)aniline were reacted to provide N2-[3,5-bis(methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.92 (d, 1H, J= 4.2 Hz), 7.20-7.10 (m, 3H), 6.92 (d, 2H, J= 2.4 Hz), 6.52 (ddd, 1H, J= 1.8, 1.8, and 7.5 Hz), 6.12 (t, 1H, J= 2.4 Hz), 4.55 (s, 4H), 3.77 (s, 6H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -47342; LCMS: purity: 92%; MS (m/e): 473(MH<sup>+</sup>).

**7.3.856 5-Fluoro-N2-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926927)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-hydroxy-5-(methoxycarbonylmethyleneoxy)aniline were reacted to produce 5-fluoro-N2-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.13 (d, 1H, J= 4.8 Hz), 7.37-7.33 (m, 1H), 7.11 (t, 1H, J= 8.4 Hz), 7.07-7.05 (m, 1H), 6.73-6.65 (m, 2H), 6.51 (dd, 1H, J= 2.1 and 8.1 Hz), 5.97 ((s, 1H), 4.59 (s, 2H), 3.67 (s, 3H); LCMS: purity: 93%; MS (m/e): 401(MH<sup>+</sup>).

**7.3.857 N2-[3-[(N-Ethylamino)carbonyloxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926928)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-[(N-ethylamino)carbonyloxy]aniline were reacted to provide N2-[3-[(N-ethylamino)carbonyloxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.92 (d, 1H, J= 3.0 Hz), 7.67-7.55 (m, 2H), 7.24 (t, 1H, J= 7.5 Hz), 7.16 (t, 1H, J= 7.5 Hz), 7.07-6.98 (m, 2H), 6.84-6.79 (m, 2H), 6.67 (m, 2H), 6.60 (d, 1H, J= 7.5 Hz), 5.22-5.14 (m, 1H), 3.36-3.27 (m, 2H), 2.95 (s, 1H), 2.88 (s, 1H), 1.20 (t, 3H, J= 7.5 Hz); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): -47012; LCMS: purity: 99%; MS (m/e): 384(MH<sup>+</sup>).

**7.3.858 5-Fluoro-N2-[3-hydroxy-5-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926929)**

A solution of 5-fluoro-N2-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (56 mg, 0.13 mmol), methylamine hydrochloride (90 mg, 1.3 mmol), and diisopropylethylamine (0.12 mL, 0.70 mmol) in methanol (2 mL) was heated at 100°C for 8h. The cooled reaction mixture was poured into 1N HCl (20 mL) saturated with NaCl, and extracted with ethyl acetate. Purification by preparative TLC (5% methanol/dichloromethane) gave the product, 5-fluoro-N2-[3-hydroxy-5-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.29 (bs, 1H), 9.16 (s, 1H), 9.01 (s, 1H), 8.06

(d, 1H, J= 3.3 Hz), 7.87 (d, 1H, J= 4.8 Hz), 7.42 (dd, 1H, J= 1.5 and 8.1 Hz), 7.13-7.05 (m, 2H), 6.89-6.81 (m, 2H), 6.45 (dd, 1H, J= 2.4 and 8.4 Hz), 5.92 (t, 1H, J= 2.4 Hz), 4.28 (s, 2H), 3.30(bs, 1H), 2.63 (s, 3H); LCMS: purity: 94%; MS (m/e): 400(MH<sup>+</sup>).

5                                    **7.3.859    N2-[3,5-Bis[(N-methylamino)carbonylmethyleneoxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926930)**

In a like manner to the preparation of 5-fluoro-N2-[3-hydroxy-5-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-[3,5-bis(methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine, methylamine hydrochloride, and diisopropylethylamine were reacted to give N2-[3,5-Bis[(N-methylamino)carbonylmethyleneoxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.91 (bs, 1H), 7.25 (t, 1H, J= 1.8 Hz), 7.14-7.11 (m, 1H), 6.98 (s, 1H), 6.97 (s, 1H), 6.55-6.50 (m, 1H), 6.26-6.23 (m, 1H), 4.39 (s, 4H), 2.81 (s, 6H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -47307; LCMS: purity: 99%; MS (m/e): 471=(MH<sup>+</sup>).

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**7.3.860    5-Fluoro-N4-[(1H)-indol-5-yl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926931)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)-indol-5-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-[(1H)-indol-5-yl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.09 (bs, 1H), 9.93 (bs, 1H), 9.67 (bs, 1H), 8.12 (d, 1H, J= 4.81 Hz), 7.94-7.82 (m, 2H), 7.37-7.22 (m, 4H), 7.13 (bs, 1H), 7.07 (t, 1H, J= 8.1 Hz), 6.58 (d, 1H, J= 7.8 Hz), 6.37 (s, 1H), 4.32 (s, 2H), 2.61 (d, 3H, J= 4.2 Hz); LCMS: purity: 92%; MS (m/e): 407(MH<sup>+</sup>).

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30                                    **7.3.861    5-Fluoro-N2-(3-hydroxyphenyl)-N4-[(1H)-indol-5-yl]-2,4-pyrimidinediamine (R926932)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-

fluoro-N4-[(1H)-indol-5-yl]-4-pyrimidineamine and 3-hydroxyaniline were reacted to provide 5-fluoro-N2-(3-hydroxyphenyl)-N4-[(1H)-indol-5-yl]-2,4-pyrimidinediamine.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.13 (s, 1H), 10.25 (bs, 1H), 9.87 (bs, 1H), 9.43 (bs, 1H), 8.16 (d, 1H, J= 5.1 Hz), 7.89 (d, 1H, J= 0.09 Hz), 7.39-7.27 (m, 3H), 7.03-6.94 (m, 2H), 6.83 (s, 1H), 6.48 (d, 1H, J= 7.5 Hz), 6.40 (t, 1H, J= 2.1 Hz); LCMS: purity: 92%; MS (m/e): 336(MH<sup>+</sup>).

**7.3.862 5-Fluoro-N4-[(1H)-indol-6-yl]-N2-[3-[(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine (R926933)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonyl]aniline were reacted to provide 5-fluoro-N4-[(1H)indol-6-yl]-N2-[3-[(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.99 (t, 1H, J= 1.8 Hz), 7.89 (d, 1H, J= 3.6 Hz), 7.78-7.76 (m, 1H), 7.70 (ddd, 1H, J= 1.2, 2.4, and 8.4 Hz), 7.50 (d, 1H, J= 9.0 Hz), 7.31 (td, 1H, J= 1.2 and 7.5 Hz), 7.23-7.17 (m, 3H), 6.43 (dd, 1H, J= 1.2 and 3.6 Hz), 2.73 (s, 3H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -47513; LCMS: purity: 99%; MS (m/e): 377(MH<sup>+</sup>).

**7.3.863 5-Fluoro-N4-[(1H)-indol-6-yl]-N2-[3-(N-morpholinocarbonyl)phenyl]-2,4-pyrimidinediamine (R926934)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-(N-morpholinocarbonyl)aniline were reacted to provide 5-fluoro-N4-[(1H)-indol-6-yl]-N2-[3-(N-morpholinocarbonyl)phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.96 (d, 1H, J= 4.8 Hz), 7.73 (t, 1H, J= 2.4 Hz), 7.66 (d, 1H, J= 1.2 Hz), 7.52 (d, 1H, J= 8.1 Hz), 7.49 (ddd, 1H, J= 0.09, 2.1, and 8.1 Hz), 7.33-7.26 (m, 2H), 7.19 (dd, 1H, J= 1.8 and 8.7 Hz), 7.12-7.06 (m, 1H), 6.45 (dd, 1H, J= 1.3 and 3.0 Hz), 3.62-3.15 (m, 8H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -46545; LCMS: purity: 91%; MS (m/e): 433(MH<sup>+</sup>).

**7.3.864 N2-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926935)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-[4-(ethoxycarbonyl)piperidino]aniline were reacted to provide N2-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.99 (d, 1H, J= 5.1 Hz), 7.64-7.58 (m, 2H), 7.52 (d, 1H, J= 8.7 Hz), 7.48 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 7.34-7.27 (m, 2H), 7.19-7.13 (m, 2H), 6.46 (dd, 1H, J= 1.2 and 4.2 Hz), 4.40-4.27 (m, 1H), 4.13 (q, 2H, J= 6.9 Hz), 3.56-3.41 (m, 1H), 2.95-2.82 (m, 2H), 2.58-2.47 (m, 1H), 1.98-1.82 (m, 1H), 1.75-7.60 (m, 1H), 1.58-1.39 (m, 2H), 1.24 (t, 3H, J= 6.9 Hz); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -46101; LCMS: purity: 90%; MS (m/e): 503(MH<sup>+</sup>).

**7.3.865 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine (R926936)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(N-methylamino)carbonyl]aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.01 (d, 1H, J= 5.4 Hz), 7.84 (t, 1H, J= 1.8 Hz), 7.68-7.61 (m, 2H), 7.45 (t, 1H, J= 8.4 Hz), 7.16-7.03 (m, 3H), 6.68 (td, 1H, J= 1.2 and 8.7 Hz), 2.90 (s, 3H); LCMS: purity: 95%; MS (m/e): 354(MH<sup>+</sup>).

**7.3.866 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-propylamino)carbonyl]phenyl]-2,4-pyrimidinediamine (R926937)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(N-propylamino)carbonyl]aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-propylamino)carbonyl]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.00 (d, 1H, J= 5.4 Hz), 7.84 (t, 1H, J= 1.8 Hz), 7.69-7.59 (m, 2H), 7.44 (t, 1H, J= 7.5 Hz), 7.16-7.05 (m, 3H), 6.67 (td, 1H, J= 2.4 and 7.2 Hz), 3.34-3.29 (m, 2H), 1.65-1.56 (m, 2H), 0.96 (t, 3H, J=

7.5 Hz);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CD}_3\text{OD}$ ): -46049; LCMS: purity: 94%; MS (m/e): 382( $\text{MH}^+$ ).

5                    **7.3.867    5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morpholinocarbonyl)phenyl]-2,4-pyrimidinediamine (R926938)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(N-morpholinocarbonyl)aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morpholinocarbonyl)phenyl]-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.93 (d, 1H,  $J = 3.6$  Hz), 7.84 (t, 1H,  $J = 1.8$  Hz), 7.62 (ddd, 1H,  $J = 1.2, 2.4$ , and 8.1 Hz), 7.32 (t, 1H,  $J = 8.4$  Hz), 7.19-7.10 (m, 3H), 6.96 (dd, 1H,  $J = 1.2$  and 7.8 Hz), 6.56 (ddd, 1H,  $J = 1.2, 3.0$ , and 6.9 Hz), 3.78-3.34 (m, 8H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CD}_3\text{OD}$ ): -47323; LCMS: purity: 100%; MS (m/e): 410( $\text{MH}^+$ ).

15                    **7.3.868    N2-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926939)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-[[4-(ethoxycarbonyl)piperidino]carbonyl]aniline were reacted to provide N2-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.92 (d, 1H,  $J = 3.6$  Hz), 7.82 (s, 1H), 7.62 (td, 1H,  $J = 1.2$  and 8.4 Hz), 7.30 (t, 1H,  $J = 8.4$  Hz), 7.19-7.09 (m, 3H), 6.93 (d, 1H,  $J = 7.5$  Hz), 6.55 (td, 1H,  $J = 1.2$  and 7.5 Hz), 4.43 (bd, 1H,  $J = 12.3$  Hz), 4.13 (q, 2H,  $J = 6.9$  Hz), 3.7 (bd, 1H,  $J = 11.7$  Hz), 3.10-2.92 (m, 2H), 2.67-2.55 (m, 1H), 2.06-1.50 (m, 4H), 1.24 (t, 1H,  $J = 6.9$  Hz);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CD}_3\text{OD}$ ): -47299; LCMS: purity: 99%; MS (m/e): 480( $\text{MH}^+$ ).

30                    **7.3.869    N4-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926940)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-4-pyrimidineamine and 3-

hydroxyaniline were reacted to provide N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.93 (d, 1H, J= 3.6 Hz), 7.89 (t, 1H, J= 1.8 Hz), 7.83 (td, 1H, J= 1.2 and 8.4 Hz), 7.41 (t, 1H, J= 7.8 Hz), 7.11-6.95 (m, 4H), 6.41 (td, 1H, J= 1.8 and 7.2 Hz), 4.44 (bd, 1H, J= 12.9 Hz), 4.10 (q, 2H, J= 7.2 Hz), 3.73 (bd, 1H, J= 12.3 Hz), 3.18-2.98 (m, 2H), 2.67-2.55 (m, 1H), 2.05-1.53 (m, 4H), 1.23 (t, 3H, J= 7.2 Hz); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -47483; LCMS: purity: 99%; MS (m/e): 480(MH<sup>+</sup>).

10                    **7.3.870    N4-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethylenoxy]phenyl]-2,4-pyrimidinediamine (R926941)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methylenoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethylenoxy]aniline were reacted to provide N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethylenoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.95 (d, 1H, J= 3.3 Hz), 7.90 (t, 1H, J= 1.8 Hz), 7.80 (ddd, 1H, J= 0.09, 2.1, 8.1 Hz), 7.39 (t, 1H, J= 7.5 Hz), 7.31 (t, 1H, J= 1.2 Hz), 7.17-7.06 (m, 3H), 6.60-6.54 (m, 1H), 4.48-4.38 (m, 3H), 4.10 (q, 2H, J= 6.9 Hz), 3.78-3.65 (m, 1H), 3.17-2.95 (m, 2H), 2.79 (s, 3H), 2.65-2.53 (m, 1H), 2.01-1.52 (m, 4H), 1.22 (t, 3H, J= 6.9 Hz); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -47309; LCMS: purity: 99%; MS (m/e): 551(MH<sup>+</sup>).

25                    **7.3.871    Reaction of 3-hydroxyaniline and 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methylenoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine and 3-hydroxyaniline were reacted to provide two products, R926942 and R926943.

30                    **7.3.872    N4-(1-Ethoxy-1,2,3,4-tetrahydronaphthalen-7-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926942)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.23 (bs, 1H), 9.14 (bs, 1H), 8.97 (bs, 1H), 8.04 (d, 1H, J= 3.6 Hz), 7.71 (dd, 1H, J= 2.4 and 7.5 Hz), 7.56 (bs, 1H), 7.14-6.98 (m, 3H), 6.93 (t, 1H, J=



8.1 Hz), 6.29 (bd, 1H, J= 7.2 Hz), 4.35 (bs, 1H), 3.59-3.36 (m, 2H), 2.69-2.60 (m, 2H), 1.89-1.78 (m, 2H), 1.72-1.56 (m, 2H), 1.08 (t, 3H, J= 6.9 Hz); LCMS: purity: 96%; MS (m/e): 395(MH<sup>+</sup>).

5                    **7.3.873    5-Fluoro-N4-(3,4-dihydronaphthalen-7-yl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926943)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.19 (bs, 2H), 9.01 (s, 1H), 8.04 (d, 1H, J= 3.6 Hz), 7.56-7.46 (m, 2H), 7.16-7.03 (m, 3H), 6.94 (t, 1H, J= 8.1 Hz), 6.46 (d, 1H, J= 9.6 Hz), 6.03 (dd, 1H, J= 1.8 and 8.1 Hz), 6.09-6.01 (m, 1H), 2.69 (t, 2H, J= 8.4 Hz), 2.28-2.20 (m, 2H); <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>): -46541; LCMS: purity: 98%; MS (m/e): 349(MH<sup>+</sup>).

10                    **7.3.874    5-Fluoro-N4-(3,4-dihydronaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926944)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-(3,4-dihydronaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.07 (d, 1H, J= 3.9 Hz), 7.53-7.45 (m, 2H), 7.32-7.29 (m, 2H), 7.11-7.01 (m, 2H), 6.49-6.40 (m, 2H), 6.08-6.00 (m, 1H), 4.32 (s, 2H), 2.69 (t, 2H, J= 8.4 Hz), 2.62 (s, 3H); LCMS: purity: 99%; MS (m/e): 420(MH<sup>+</sup>).

20                    **7.3.875    N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926945)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-hydroxyaniline were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.91 (d, 1H, J= 5.4 Hz), 7.71 (d, 1H, J= 2.4 Hz), 7.58 (dd, 1H, J= 3.0 and 9.0 Hz), 7.15 (t, 1H, J= 8.4 Hz), 7.06 (d, 1H, J= 8.7 Hz), 6.92 (td, 1H, J= 1.8 and 9.9 Hz), 6.88 (t, 1H, J= 1.8 Hz), 6.61 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 3.89 (s, 3H), ; <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD): -46612; LCMS: purity: 98%; MS (m/e): 362(MH<sup>+</sup>).

**7.3.876 N2,N4-Bis(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926946)**

In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-methoxyaniline were reacted to provide N2,N4-Bis(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.90 (bs, 1H), 9.68 (bs, 1H), 8.16 (d, 1H, J= 4.8 Hz), 7.72 (d, 1H, J= 2.4 Hz), 7.65 (d, 1H, J= 2.1 Hz), 7.58 (dd, 1H, J= 2.4 and 9.0 Hz), 7.38 (dd, 1H, J= 2.7 and 9.3 Hz), 7.12 (d, 1H, J= 8.7 Hz), 7.12 (d, 1H, J= 8.7 Hz), 7.05 (d, 1H, J= 8.7 Hz), 3.83 (s, 3H), 3.79 (s, 3H); LCMS: purity: 99%; MS (m/e): 410(MH<sup>+</sup>).

**7.3.877 5-Fluoro-N4-(1,2,3,4-tetrahydro-1-oxonaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926947)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.89 (bs, 1H), 9.55 (bs, 1H), 8.17 (d, 1H, J= 4.2 Hz), 8.04-7.93 (m, 3H), 7.32 (d, 1H, J= 8.7 Hz), 7.25-7.16 (m, 2H), 7.09 (t, 1H, J= 7.5 Hz), 6.52 (dd, 1H, J= 2.4 and 8.1 Hz), 4.28 (s, 2H), 2.90 (t, 2H, J= 6.0 Hz), 2.63 (d, 3H, J= 4.8 Hz), 2.59 (t, 2H, J= 6.6 Hz), 2.02 (t, 2H, J= 6.6 Hz); LCMS: purity: 93%; MS (m/e): 436(MH<sup>+</sup>).

**7.3.878 5-Fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxyiminonaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926948)**

A solution of 5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (42 mg, 0.095 mmole) and hydroxylamine hydrochloride (8.5 mg, 0.12 mmole) in DMF (1 mL) was heated at 60°C for 12h. The reaction mixture was cooled to rt and then poured into brine (20 mL). A brown solid was collected by suction filtration and further purified by reverse phase chromatography to provide 5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxyiminonaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.13-8.05 (m, 2H), 7.99-7.92 (m, 2H), 7.77-7.72 (m, 1H), 7.33-7.21

(m, 2H), 7.14 (d, 1H, J= 8.7 Hz), 7.10-7.02 (m, 1H), 6.47 (dd, 1H, J= 2.4 and 7.5 Hz), 4.30 (s, 2H), 2.90 (t, 1H, J= 6.0 Hz), 2.70-2.40 (m, 6H), 2.07-1.98 (m, 1H), 1.74 (t, 1H, J= 6.6 Hz); LCMS: purity: 96%; MS (m/e): 451(MH<sup>+</sup>).

5                                **7.3.879    5-Fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926949)**

To a 0°C suspension of 5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (50mg, 0.11 mmol) in anhydrous THF (2.0 mL) was added lithiumborohydride (5 mg, 0.23 mmole).  
 10    The reaction mixture was warmed to rt, stirred for 8h, and then quenched with methanol. The reaction mixture was poured into water and then extracted with ethyl acetate. Purification by preparative TLC (5% methanol/dichloromethane) provided 5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. LCMS: purity: 96%;  
 15    MS (m/e): 438(MH<sup>+</sup>).

**7.3.880    N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[2-(methoxycarbonyl) benzofuran-5-yl]-2,4-pyrimidinediamine (R926950)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(methoxycarbonyl)benzofuran were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.34 (bs, 2H), 8.10-8.07 (m, 2H), 7.78 (t, 1H, J= 2.7 Hz), 7.66-7.53 (m, 4H), 7.12 (d, 1H, J= 9.3 Hz), 3.87 (s, 3H), 3.85 (s, 3H);  
 25    LCMS: purity: 99%; MS (m/e): 443(MH<sup>+</sup>).

**7.3.881    N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine (R926951)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2,3-dihydro-2-(methoxycarbonyl)benzofuran were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.31

(bs, 1H), 10.04 (bs, 1H), 8.21 (d, 1H, J= 4.8 Hz), 7.75 (t, 1H, J= 3.0 Hz), 7.54 (td, 1H, J= 3.0 and 9.0 Hz), 7.34 (s, 1H), 7.20-7.15 (m, 2H), 6.80 (d, 1H, J= 8.1 Hz), 5.38-5.31 (m, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 3.49 (dd, 1H, J= 11.1 and 16.5 Hz); LCMS: purity: 99%; MS (m/e): 446(MH<sup>+</sup>).

5                                    **7.3.882    N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine (R926953)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2,3-dihydro-2-(methoxycarbonyl)benzofuran were reacted to produce N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.99 (bs, 1H), 9.49 (bs, 1H), 8.18 (d, 1H, J= 4.5 Hz), 8.08 (t, 1H, J= 2.4 Hz), 7.81-7.74 (m, 1H), 7.49 (d, 1H, J= 8.1 Hz), 7.42 (s, 1H), 7.20 (d, 1H, J= 8.1 Hz), 6.78 (d, 1H, J= 8.7 Hz), 5.36 (m, 1H), 3.80-3.47 (m, 4H), 3.20 (dd, 1H, J= 6.0 and 16.5 Hz); LCMS: purity: 100%; MS (m/e): 500(MH<sup>+</sup>).

**7.3.883    N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine (R926954)**

20                                    In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine, methylamine hydrogen chloride salt, and diisopropylethylamine were reacted to provide N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.59 (s, 1H), 9.10 (s, 2H), 8.13-8.10 (m, 1H), 8.08-7.98 (m, 1H), 7.82 (d, 1H, J= 8.1 Hz), 7.48-7.42 (m, 2H), 7.24 (d, 1H, J= 8.7 Hz), 6.72 (d, 1H, J= 8.7 Hz), 5.06 (dd, 1H, J= 5.4 and 9.3 Hz), 3.39 (dd, 1H, J= 10.5 and 15.6 Hz), 3.15 (dd, 1H, J= 6.3 and 15.9 Hz), 2.59 (d, 3H, J= 4.5 Hz); LCMS: purity: 95%; MS (m/e): 499(MH<sup>+</sup>).

**7.3.884 N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine (R926955)**

In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine, methylamine hydrochloride, and diisopropylethylamine were reacted to provide N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.24 (s, 1H), 8.99 (s, 2H), 8.02 (d, 1H, J= 3.0 Hz), 7.80-7.75 (m, 1H), 7.63 (d, 1H, J= 9.0 Hz), 7.47 (s, 1H), 7.23 (d, 1H, J= 8.1 Hz), 7.07 (d, 1H, J= 8.7 Hz), 6.69 (d, 1H, J= 8.1 Hz), 5.05 (dd, 1H, J= 2.1 and 9.9 Hz), 3.37 (dd, 1H, J= 10.5 and 15.9 Hz), 3.13 (dd, 1H, J= 6.0 and 15.9 Hz), 2.59 (d, 3H, J= 4.5 Hz); LCMS: purity: 95%; MS (m/e): 445(MH<sup>+</sup>).

**7.3.885 5-Fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R926956)**

In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine, methylamine hydrochloride, and diisopropylethylamine were reacted to provide 5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.11 (s, 1H), 8.92 (s, 1H), 8.06-7.98 (m, 1H), 7.97 (d, 1H, J= 4.2 Hz), 7.60-7.52 (m, 3H), 7.20 (d, 1H, J= 8.1 Hz), 6.85 (d, 2H, J= 8.7 Hz), 6.67 (d, 1H, J= 9.0 Hz), 5.04 (dd, 1H, J= 5.7 and 9.9 Hz), 4.56 (quintet, 1H, J= 6.6 Hz), 3.36 (dd, 1H, J= 10.5 and 16.5 Hz), 3.10 (dd, 1H, J= 5.7 and 15.3 Hz), 2.59 (d, 1H, J= 4.5 Hz), 1.24 (d, 6H, J= 6.6 Hz); LCMS: purity: 96%; MS (m/e): 438(MH<sup>+</sup>).

**7.3.886 N2,N4-Bis(3-phenylphenyl)-2,4-pyrimidinediamine (R925809)**

In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-aminobiphenyl were reacted to provide N2,N4-Bis(3-phenylphenyl)-2,4-pyrimidinediamine. LCMS: purity: 98%; MS (m/e): 415(MH<sup>+</sup>).

**7.3.887 2-Dimethylamine-5-fluoro-N4-(thyrosinyl methyl ester) pyrimidine (R940110)**

A solution of 2,4-dichloro-5-fluoropyrimidine (0.03 g, 0.18 mmol) and L-tyrosine methyl ester (0.14 g, 0.7 mmol) in DMF was heated at 100°C for 3 days. The reaction mixture was cooled to room temperature and diluted with H<sub>2</sub>O (10 mL). Upon saturation with sodium chloride it was extracted with ethyl acetate (3 x 15 mL), dried over anhydrous sodium sulfate and the solvent was removed. The resulting residue was filtered through a pad of silica gel (200-400 mesh, hexanes/EtOAc 2/8) to obtain 2-dimethylamine-5-fluoro-N4-(thyrosinyl methyl ester) pyrimidine **R940110**. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.76 (1H, d, *J* = 3.2 Hz), 7.00 (2H, d, *J* = 7.5 Hz), 6.76 (2H, d, *J* = 7.5 Hz), 5.20 (1H, d, *J* = 7.5 Hz), 4.90 (1H, q, *J* = 5.0 Hz), 3.71 (3H, s), 3.14 (2H, m), 3.08 (6H, s); purity: 98%; MS (m/e): 335 (M+H).

**7.3.888 5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine (R940299)**

To a solution of 2-chloro-5-fluoro-N4-(3-aminocarbonylphenyl)-4-pyrimidineamine (0.050g, 0.18 mmol) in (2 mL) was added 3-(methylaminocarbonylmethyleneoxy)aniline (0.1g, 0.5 mmol). The mixture was heated in a sealed tube at 100 °C for 24h. The resulting reaction was diluted with H<sub>2</sub>O (10 mL), acidified with 2N HCl (pH >2), saturated with sodium chloride and the resulting solid was filtered to give the desired product 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine **R940299**. Purification can be done by filtration through a pad of silica gel using 1-5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> or by crystallization using an appropriate solvent system. Alternatively, the reaction of equimolar amount of 2-chloro-5-fluoro-N4-(3-aminocarbonylphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline in MeOH in a pressure tube at 110 °C for 24h or, in EtOH using microwave at 175 °C for 30-60 min followed by aqueous work up, also gave the desired product. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.79 (1H, s), 9.49 (1H, s), 8.26 (1H, d, *J* = 3.9 Hz), 8.15 (1H, t, *J* = 1.8 Hz), 8.10-8.02 (3H, m), 7.68 (1H, d, *J* = 7.5 Hz), 7.51 (1H, t, *J* = 7.9 Hz), 7.48 (1H, s), 7.38 (2H, m), 7.20 (1H, t, *J* = 8.4 Hz), 6.60 (1H, d, *J* = 9.3 Hz), 4.45 (2H, s), 2.74 (3H, d, *J* = 4.8 Hz); purity: 95%; MS (m/e): 411 (MH+).

**7.3.889 5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940300)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940300**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.66 (1H, s), 9.45 (1H, s), 8.21 (1H, d, *J* = 3.9 Hz), 8.06 (2H, m), 8.01 (1H, t, *J* = 2.7 Hz), 7.35 (2H, m), 7.23 (1H, d, *J* = 9 Hz), 7.18 (1H, t, *J* = 8.1 Hz), 6.60 (1H, d, *J* = 7.8 Hz), 4.45 (2H, s), 3.91 (3H, s), 3.84 (3H, s), 2.74 (3H, d, *J* = 3.6 Hz); purity: 93%; MS (*m/e*): 456 (MH<sup>+</sup>).

**7.3.890 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940301)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-methyloxycarbonyl-4-methoxyaniline were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940301**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.93 (1H, s), 9.79 (1H, s), 9.54 (1H, s), 8.26 (1H, s, *J* = 4.5 Hz), 7.92 (1H, s), 7.81 (1H, dd, *J* = 9.3 Hz, *J* = 2.7 Hz), 7.32 (1H, d, *J* = 8.1 Hz), 7.20-7.13 (3H, m), 6.64 (1H, d, *J* = 8.1 Hz), 3.89 (3H, s), 3.84 (3H, s); purity: 97%; MS (*m/e*): 385 (MH<sup>+</sup>).

**7.3.891 5-Fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine (R940304)**

A mixture of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine (0.15 g, 0.4 mmol), methylamine hydrochloride (0.324 g, 48 mmol) and diisopropylethylamine (0.84 mL, 48 mmol) in MeOH (2 mL) was heated in a sealed tube at 100 °C for 24h (followed by TLC). The reaction was cooled to room temperature and diluted with H<sub>2</sub>O (20 mL). The solid was filtered, washed with H<sub>2</sub>O and dried to obtain 5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine **R940304**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.65 (1H, s), 8.48 (1H, s), 8.29 (2H, m), 7.93 (1H, m),

7.28 (1H, d,  $J = 9$  Hz), 4.00 (3H, s), 2.94 (3H, s), 2.90 (3H, d,  $J = 4.5$  Hz) ; purity: 90% ; MS (m/e): 306 (MH<sup>+</sup>);

5                    **7.3.892    5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940306)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to yield

10    5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940306**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.28 (1H, s), 9.21 (1H, s), 8.12 (1H, d,  $J = 3.9$  Hz), 8.06 (1H, d,  $J = 2.7$  Hz), 7.99 (1H, m), 7.89 (1H, dd,  $J = 9.3$  Hz,  $J = 2.7$  Hz), 7.52 (1H, q,  $J = 4.9$  Hz), 7.41 (1H, t,  $J = 2.1$  Hz), 7.37 (1H, d,  $J = 7.5$  Hz), 7.10 (1H, t,  $J = 8.1$  Hz), 6.83 (1H, d,  $J = 9$  Hz), 6.53 (1H, dd,  $J = 8.1$  Hz,  $J = 1.8$  Hz),

15    4.40 (2H, s), 3.82 (3H, s), 2.96 (3H, d,  $J = 5.1$  Hz), 2.73 (3H, d,  $J = 4.5$  Hz) ; purity: 93% ; MS (m/e): 455 (MH<sup>+</sup>).

**7.3.893    (R)-N2-[3-(dihydroxypropylaminocarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine (R940307)**

20                    In like manner to the preparation of 5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine, 5-fluoro-N4-(3-isopropylphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and (R)-3-amino-1,2-propanediol were reacted to give (R)-N2-[3-(N-2,3-

25    dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine **R940307**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.96 (1H, s), 9.80 (1H, s), 8.29 (1H, d,  $J = 4.5$  Hz), 7.98 (1H, t,  $J = 5.5$  Hz), 7.77 (1H, d,  $J = 7.2$  Hz), 7.57 (1H, s), 7.37 (1H, t,  $J = 7.8$  Hz), 7.30-7.22 (3H, m), 7.12 (1H, d,  $J = 7.8$  Hz), 6.70 (1H, d,  $J = 7.5$  Hz), 4.47 (2H, s), 3.62 (1H, m), 3.38 (3H, m), 3.15 (1H, m), 2.94 (1H, quint,  $J = 6.9$  Hz), 1.27 (6H, d, 6.9 Hz) ; purity: 99%; MS (m/e): 469 (M), 470 (MH<sup>+</sup>).



**7.3.894 N4-(3-*tert*-Butylphenyl)-5-fluoro-N2-[3-(1,1-dimethyl-2-hydroxyethylaminocarbonylmethyleneoxy)-phenyl]-2,4-pyrimidinediamine (R940308)**

In like manner to the preparation of 5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 2-amino-2-methyl-1-propanol were reacted to give N4-(3-*tert*-butylphenyl)-5-fluoro-N2-[3-(1,1-dimethyl-2-hydroxyethylaminocarbonylmethyleneoxy)-phenyl]-2,4-pyrimidinediamine **R940308**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.38 (1H, s), 9.28 (1H, s), 8.20 (1H, d, *J* = 3.9 Hz), 7.99 (1H, d, *J* = 7.5 Hz), 7.60 (1H, t, *J* = 2.1 Hz), 7.46 (1H, s), 7.37 (2H, t, *J* = 7.9 Hz), 7.30 (1H, s), 7.19 (2H, t, *J* = 7.9 Hz), 6.56 (1H, dd, *J* = 7.5 Hz, *J* = 1.5 Hz), 5.06 (1H, t, *J* = 5.7 Hz), 4.37 (2H, s), 3.40 (2H, m), 1.36 (9H, s), 1.32 (6H, s); purity: 93%; MS (*m/e*): 482 (MH<sup>+</sup>).

**7.3.895 N4-(3-Aminomethylenepheryl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940309)**

A mixture of N4-[3-(*N-tert*-butoxycarbonyl-*N*-aminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline in MeOH was heated in a sealed tube at 100 °C for 12h. The reaction was cool to room temperature and the solvent was removed under reduce pressure. The resulting residue was filtered through a pad of silica gel (200-400 mesh, EtOAc/MeOH (2M NH<sub>3</sub>) 95:5) to obtain the desired product N4-(3-aminomethylenepheryl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940309**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.41 (1H, s), 9.23 (1H, s), 8.20 (1H, d, *J* = 3.9 Hz), 8.00 (1H, m), 7.78 (1H, s), 7.72 (1H, d, *J* = 7.2 Hz), 7.46 (1H, s), 7.42-7.33 (2H, m), 7.21 (1H, t, *J* = 7.8 Hz), 7.14 (1H, d, *J* = 7.8 Hz), 6.59 (1H, dd, *J* = 8.1 Hz, *J* = 2.4 Hz), 4.42 (2H, s), 3.79 (2H, s), 2.74 (3H, d, *J* = 4.8 Hz); purity: 98%; MS (*m/e*): 397 (MH<sup>+</sup>).

**7.3.896 N4-[3-(2-(N4-(3-aminomethylenepheryl)-5-fluoro-4-pyrimidineamine)-*N*-methylaminomethylene)-phenyl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidineamine (R940311)**

A mixture of N4-[3-(*N*-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (0.05 g, 0.18 mmol) and 3-(methylaminocarbonylmethyleneoxy)aniline (0.04 g, 0.22 mmol) in EtOH (0.5 mL), was heated at 175 °C for 35 min using microwave. An aqueous work up gave the desired N4-[3-(2-(N4-(3-aminomethylenepheryl)-5-fluoro-4-

pyrimidineamine)-N-methylaminomethylene)-phenyl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidineamine **R940311**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.48 (1H, s), 9.31 (1H, s), 9.26 (1H, s), 8.20 (1H, d, *J* = 3.6 Hz), 8.10-8.05 (4H, m), 7.62 (1H, s), 7.49 (2H, m), 7.41 (1H, t, *J* = 8.1 Hz), 7.36 (2H, m), 7.22 (1H, t, *J* = 8.4 Hz), 7.17 (1H, t, *J* = 8.4 Hz), 7.06 (1H, d, *J* = 7.5 Hz), 6.59 (1H, dd, *J* = 8.4 Hz, *J* = 2.4 Hz), 6.54 (1H, dd, *J* = 7.8 Hz, *J* = 2.4 Hz), 4.93 (2H, s), 4.46 (2H, s), 4.45 (2H, s), 3.28 (3H, d, *J* = 3 Hz), 2.73 (6H, m) ; purity: 98%; MS (m/e) : 684 (M), 685 (MH<sup>+</sup>).

**7.3.897 5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-*iso*-propylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940312)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-*N-iso*-propylaminomethylene-4-methoxyphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-*iso*-propylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940312**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.09 (1H, s), 9.88 (1H, s), 8.25 (1H, d, *J* = 4.8 Hz), 8.07 (1H, d, *J* = 2.7 Hz), 8.05 (1H, m), 7.81 (1H, dd, *J* = 9 Hz, *J* = 2.7 Hz), 7.63 (1H, s), 7.25 (2H, m), 7.17 (1H, t, *J* = 8.25 Hz), 6.91 (1H, d, *J* = 9 Hz), 6.68 (1H, d, *J* = 8.1 Hz), 4.42 (2H, s), 3.85 (1H, m), 3.81 (3H, s), 2.72 (3H, d, *J* = 4.2 Hz), 1.30 (6H, d, *J* = 6 Hz) ; purity: 97% ; MS (m/e): 483 (MH<sup>+</sup>).

**7.3.898 5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-[3-(*N*-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine (R940314)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(*N*-morpholinomethylene)-4-methoxyphenyl]-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-[3-(*N*-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine **R940314**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.33 (1H, s), 9.21 (1H, s), 8.15 (1H, d, *J* = 3.6 Hz), 8.04 (1H, d, *J* = 4.8 Hz), 7.82 (1H, dd, *J* = 9 Hz, *J* = 2.7 Hz), 7.57 (1H, d, *J* = 3 Hz), 7.47 (1H, t, *J* = 1.95 Hz), 7.34 (1H, m), 7.18 (1H, t, *J* = 8.1 Hz), 7.04 (1H, d, *J* = 9 Hz), 6.56 (1H, dd, *J* = 8.4 Hz, *J* = 2.1

Hz), 4.40 (2H, s), 3.86 (3H, s), 3.63 (4H, t,  $J = 4.5$  Hz), 3.53 (2H, s), 2.74 (3H, d,  $J = 4.5$  Hz), 2.46 (4H, m) ; purity: 97%; MS (m/e): 497 (MH<sup>+</sup>).

5                    **7.3.899    N2-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine (R940316)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-4-pyrimidineamine and 4-amino-2-chloro-6-methylphenol were reacted to  
 10    produce N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine R940316. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.28 (1H, s), 9.01 (1H, s), 8.65 (1H, s), 8.11 (1H, d,  $J = 3.9$  Hz), 7.76 (1H, dd,  $J = 9$  Hz,  $J = 3$  Hz), 7.61 (1H, d,  $J = 2.4$  Hz), 7.50 (1H, d,  $J = 2.7$  Hz), 7.30 (1H, d,  $J = 2.1$  Hz), 7.04 (1H, d,  $J = 8.7$  Hz), 3.87 (3H, s), 3.63 (4H, t,  $J = 4.3$  Hz), 3.52 (2H, s), 2.45 (4H,  
 15    m), 2.17 (3H, s) ; purity: 97% ; MS (m/e): 474 (MH<sup>+</sup>).

**7.3.900    N4-(3-N-methylaminomethylenephenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940317)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N4-[3-(N-*tert*-butoxycarbonyl-N-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-(3-N-methylaminomethylenephenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine R940317. <sup>1</sup>H NMR  
 25    (DMSO-d<sub>6</sub>): δ 9.41 (1H, s), 9.31 (1H, s), 9.29 (1H, s), 8.20 (1H, d,  $J = 3$  Hz), 8.05 (1H, m), 7.80 (1H, d,  $J = 7.8$  Hz), 7.74 (1H, s), 7.45-7.35 (3H, m), 7.21 (1H, t,  $J = 8.1$  Hz), 7.13 (1H, d,  $J = 7.5$  Hz), 6.59 (1H, d,  $J = 9.6$  Hz), 4.43 (2H, s), 3.71 (2H, s), 2.75 (3H, d,  $J = 4.2$  Hz), 2.35 (3H, s) ; purity: 83.9% ; MS (m/e): 411 (MH<sup>+</sup>).

30                    **7.3.901    N2-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-piperazinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine (R940318)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-

pyrimidinediamine, N4-[3-(N-piperazinomethylene)-4-methoxyphenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 4-amino-2-chloro-6-methylphenol were reacted to produce N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-piperazinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine **R940318**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.27 (1H, s), 9.00 (1H, s), 8.10 (1H, d, *J* = 3.6 Hz), 7.75 (1H, dd, *J* = 8.7 Hz, *J* = 2.7 Hz), 7.61 (1H, d, *J* = 2.4 Hz), 7.49 (1H, d, *J* = 2.4 Hz), 7.31 (1H, d, *J* = 2.4 Hz), 7.03 (1H, d, *J* = 9 Hz), 3.86 (3H, s), 3.49 (2H, s), 2.75 (4H, t, *J* = 4.65 Hz), 2.39 (4H, m), 2.17 (3H, s) ; purity: 95%; MS (m/e): 473 (MH<sup>+</sup>).

10                                    **7.3.902    N4-(3-(N-*tert*-Butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940319)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N4-(3-(N-*tert*-butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-(3-(N-*tert*-butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940319**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.44 (1H, s), 8.95 (1H, s), 8.15 (1H, d, *J* = 3.6 Hz), 8.06 (1H, m), 7.83 (1H, m), 7.74 (1H, m), 7.56 (1H, m), 7.37 (1H, m), 7.20 (1H, t, *J* = 7.9 Hz), 7.02 (1H, d, *J* = 9.3 Hz), 6.57 (1H, d, *J* = 7.8 Hz), 4.44 (2H, s), 4.42 (1H, m), 4.33 (2H, s), 3.89 (3H, s), 2.74 (3H, d, *J* = 4.8 Hz), 1.52-1.30 (9H, m), 1.16 (6H, d, *J* = 6.9 Hz) ; purity: 98% ; MS (m/e): 569 (MH<sup>+</sup>).

25                                    **7.3.903    N4-(3-N,N-Dimethylaminomethylene-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940321)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-N,N-dimethylaminomethylene-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-(3-N,N-dimethylaminomethylene-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940321**.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.32 (1H, s), 9.23 (1H, s), 8.14 (1H, d, *J* = 3.9 Hz), 8.05 (1H, m), 7.83 (1H, dd, *J* = 8.7 Hz, *J* = 2.4 Hz), 7.55 (1H, d, *J* = 2.4 Hz), 7.45 (1H, s), 7.36 (1H, d, *J* = 8.4 Hz), 7.18 (1H, t, *J* = 8.1 Hz), 7.03 (1H, d, *J* = 9 Hz), 6.56 (1H, dd, *J* = 7.2 Hz, *J* = 1.5 Hz), 4.41 (2H, s), 3.86 (3H, s), 2.73 (3H, d, *J* = 4.5 Hz), 2.24 (6H, s) ; purity: 91.8% ;  
 5 MS (m/e): 455 (MH<sup>+</sup>).

**7.3.904 N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940323)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940323**.

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.70 (1H, s), 9.45 (1H, s), 9.19 (1H, s), 8.17 (1H, d, *J* = 3.9 Hz), 8.05 (1H, m), 7.43-7.34 (4H, m), 7.17 (1H, t, *J* = 8.25 Hz), 6.98 (1H, d, *J* = 8.4 Hz), 6.56 (1H, dd, *J* = 7.8 Hz, *J* = 2.1 Hz), 4.25 (2H, s), 2.74 (3H, d, *J* = 4.5 Hz), 1.5 (6H, s) ; purity: 98.7% ; MS (m/e): 467 (MH<sup>+</sup>).

20 **7.3.905 N4-[3-Dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940337)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940337**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.28 (1H, s), 9.20 (1H, s), 8.34 (1H, dd, *J* = 4.8 Hz, *J* = 1.2 Hz), 8.14 (1H, d, *J* = 3.8 Hz), 8.03 (1H, m), 7.64-7.60 (2H, m), 7.51-7.46 (3H, m), 7.37 (1H, d, *J* = 8.4 Hz), 7.17 (1H, t, *J* = 8.1 Hz), 6.94-6.91 (2H, m), 6.55 (1H, dd, *J* = 8.4 Hz, *J* = 3 Hz), 4.42 (2H, s), 3.93 (2H, s), 2.74 (3H, d, *J* = 4.5 Hz), 1.32 (6H, s) ; purity: 98.2% ; MS (m/e): 530 (MH<sup>+</sup>);

**7.3.906 N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine (R940338)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 5-amino-1-methyl-1-indazole were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine **R940338**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.73 (1H, s), 9.39 (1H, s), 9.17 (1H, s), 8.21 (1H, s), 8.16 (1H, d, *J* = 3.9 Hz), 7.87 (1H, s), 7.56 (2H, m), 7.41 (1H, m), 7.32 (1H, s), 7.00 (1H, d, *J* = 8.4 Hz), 4.07 (3H, s), 1.51 (6H, s); purity: 99.2%; MS (*m/e*): 434 (MH<sup>+</sup>).

**7.3.907 N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R921303)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R921303**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.05 (1H, s), 9.67 (1H, s), 9.27 (1H, s), 8.24 (1H, d, *J* = 3.6 Hz), 8.05 (1H, m), 7.73-7.68 (1H, m), 7.56 (1H, t, *J* = 2.7 Hz), 7.50 (1H, s), 7.36 (2H, d, *J* = 8.7 Hz), 7.19 (1H, t, *J* = 8.2 Hz), 6.58 (1H, dd, *J* = 8.4 Hz, *J* = 2.4 Hz), 4.34 (2H, s), 2.74 (3H, d, *J* = 4.5 Hz); <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): δ -21643, -46385; purity: 100%; MS (*m/e*): 475 (MH<sup>+</sup>).

**7.3.908 N4-[(2,2-Dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940345)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-N2-[3-

(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940345**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 11.23 (1H, s), 9.69 (1H, s), 9.54 (1H, s), 8.50 (1H, s), 8.25 (1H, d, *J* = 3.3 Hz), 8.06 (1H, m), 7.96 (1H, t, *J* = 2.5 Hz), 7.41-7.36 (2H, m), 7.24 (1H, t, *J* = 8.25 Hz), 6.34 (1H, d, *J* = 8.7 Hz), 4.47 (2H, s), 2.74 (3H, d, *J* = 3.3 Hz), 1.53 (6H, s) ; purity: 98.4% ;  
 5 MS (m/e): 468 (MH<sup>+</sup>).

**7.3.909 N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940346)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine **R940346**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.75 (1H, s), 8.25 (1H, d, *J* = 4.5 Hz), 7.42-7.37 (1H, m), 7.34 (1H, s), 7.10 (3H, m), 7.00 (1H, d, *J* = 8.4 Hz), 6.53 (1H, m), 1.50 (6H, s) ; purity: 97.5% ; MS (m/e): 396 (MH<sup>+</sup>).

**7.3.910 N4-[(2,2-Dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940347)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940347**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 11.20 (1H, s), 9.46 (1H, s), 8.26 (1H, d, *J* = 3.6 Hz), 8.06 (1H, s), 7.71 (1H, m), 7.49 (1H, d, *J* = 8.4 Hz), 7.45 (1H, s), 7.38 (1H, d, *J* = 9 Hz), 7.21 (1H, t, *J* = 8.1 Hz), 6.61 (1H, d, *J* = 8.7 Hz), 4.47 (2H, s), 2.74 (3H, s), 1.52 (6H, s); purity: 100% ; MS (m/e): 468 (MH<sup>+</sup>).

**7.3.911 N4-[3-Dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940348)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-

pyrimidinediamine, 2-chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine **R940348**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.25 (1H, s), 9.23 (1H, s), 9.02 (1H, s), 8.34 (1H, d, *J* = 4.5 Hz), 8.11 (1H, d, *J* = 3.3 Hz), 7.62 (2H, m), 7.52 (2H, m), 7.22 (1H, s), 7.19 (1H, d, *J* = 7.5 Hz), 7.03 (1H, t, *J* = 7.9 Hz), 6.93 (2H, m), 6.38 (1H, d, *J* = 7.8 Hz), 3.93 (2H, s), 1.32 (6H, s) ; purity: 96.5%.

**7.3.912 N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940349)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine **R940349**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.03 (1H, s), 9.63 (1H, s), 9.26 (1H, s), 9.09 (1H, s), 8.21 (1H, d, *J* = 3.6 Hz), 7.70 (1H, dd, *J* = 9 Hz, *J* = 2.4 Hz), 7.59 (1H, d, *J* = 2.7 Hz), 7.34 (1H, d, *J* = 9.3 Hz), 7.26 (1H, s), 7.16 (1H, d, *J* = 7.8 Hz), 7.04 (1H, t, *J* = 8.2 Hz), 6.41 (1H, d, *J* = 10.2 Hz) ; <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): δ -21646, -46516 ; purity: 95.8% ; MS (m/e): 404 (MH<sup>+</sup>);

**7.3.913 N2,N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine (R940350)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 6-amino-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one were reacted to produce N2,N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine **R940350**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.68 (1H, s), 10.62 (1H, s), 9.38 (1H, s), 9.04 (1H, s), 8.11 (1H, d, *J* = 3.6 Hz), 7.46 (1H, dd, *J* = 8.1 Hz, *J* = 1.8 Hz), 7.33-7.26 (3H, m), 6.95 (1H, d, *J* = 8.7 Hz), 6.84 (1H, d, *J* = 8.4 Hz), 1.49 (6H, s), 1.45 (6H, s) ; purity: 95.4% ; MS (m/e): 479 (MH<sup>+</sup>).



**7.3.914 N2-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine (R940351)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 6-amino-2,2-difluoro-4H-benzo[1,4]oxazin-3-one were reacted to produce N2-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine **R940351**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 11.99 (1H, s), 10.74 (1H, s), 9.64 (1H, s), 9.50 (1H, s), 8.19 (1H, d, *J* = 3.9 Hz), 7.50 (2H, m), 7.43 (1H, dd, *J* = 8.4 Hz, *J* = 1.8 Hz), 7.32 (1H, s), 7.20 (1H, d, *J* = 9.3 Hz), 6.98 (1H, d, *J* = 8.7 Hz), 1.49 (6H, s) ; purity: 94.77% ; MS (*m/e*): 487 (MH<sup>+</sup>).

**7.3.915 N2,N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine (R940352)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 6-amino-2,2-difluoro-4H-benzo[1,4]oxazin-3-one were reacted to produce N2,N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine **R940352**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.08 (1H, s), 12.00 (1H, s), 9.72 (1H, s), 9.44 (1H, s), 8.23 (1H, d, *J* = 3.6 Hz), 7.73 (1H, dd, *J* = 11.1 Hz, *J* = 1.5 Hz), 7.6 (1H, s), 7.56 (1H, s), 7.51 (1H, dd, *J* = 9.6 Hz, *J* = 2.4 Hz), 7.35 (1H, d, *J* = 9 Hz), 7.24 (1H, d, *J* = 8.7 Hz); <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): δ -21670, -21722, -4651 ; purity: 100% ; MS (*m/e*): 495 (MH<sup>+</sup>).

**7.3.916 N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R940353)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and methyl 5-aminobenzofuran-2-carboxylate were reacted to produce N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine **R940353**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):

$\delta$  12.05 (1H, s), 9.69 (1H, s), 9.43 (1H, s), 8.28 (1H, s), 8.25 (1H, d,  $J$  = 3.6 Hz), 7.40-7.64 (4H, m), 7.54 (1H, s), 7.38 (1H, d,  $J$  = 9 Hz), 3.97 (3H, s) ;  $^{19}\text{F}$  NMR (DMSO- $d_6$ ):  $\delta$  -21707, -46489 ; purity: 97.77% ; MS (m/e): 486 (MH $^+$ ).

5                    **7.3.917    N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R940354)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and methyl 5-aminobenzofuran-2-carboxylate were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine **R940354**.  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  10.75 (1H, s), 9.67 (1H, s), 9.53 (1H, s), 8.25 (1H, s), 8.21 (1H, d,  $J$  = 4.2 Hz), 7.66 (2H, s), 7.59 (1H, s), 7.31 (1H, d,  $J$  = 8.7 Hz), 7.26 (1H, s), 7.03 (1H, d,  $J$  = 8.1 Hz), 3.97 (3H, s), 1.52 (6H, s) ; purity: 95.58% ; MS (m/e): 478 (MH $^+$ ).

**7.3.918    N2,N4-Bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950244)**

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ( $\text{CHCl}_3$ :Acetone, 2:1) to give N2,N4-bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine.  $^1\text{H}$  NMR (MeOD, 300 MHz):  $\delta$  8.65 (d, 1H,  $J$  = 2.4 Hz), 7.15-7.58 (m, 8H), 2.24 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H); LCMS: ret. time: 17.03 min.; purity: 87.0%; MS (m/e): 478.89 (MH $^+$ ).

25                    **7.3.919    N4-(3-N,N-Diacetylaminophenyl)-N2-(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950245)**

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ( $\text{CHCl}_3$ :Acetone, 2:1) to give N4-(3-N,N-diacetylaminophenyl)-N2-(3-N-acetylaminophenyl)-5-fluoro-N2,N4-

pyrimidinediacetylamine.  $^1\text{H}$  NMR (MeOD, 300 MHz):  $\delta$  8.65 (d, 1H,  $J = 2.4$  Hz), 7.03-7.66 (m, 8H), 2.21 (s, 6H), 2.14 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H); LCMS: ret. time: 19.27 min.; purity: 92.6%; MS (m/e): 521.01 ( $\text{MH}^+$ ).

5                                **7.3.920    N4-(3-N-Acetylamino-phenyl)-N2-(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950246)**

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ( $\text{CHCl}_3$ :Acetone, 2:1) to give N4-[3-N-acetylamino-phenyl]-N2-(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine.  $^1\text{H}$  NMR (MeOD, 300 MHz):  $\delta$  8.66 (d, 1H,  $J = 2.4$  Hz), 6.88-7.57 (m, 8H), 2.22 (s, 6H), 2.11 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H); LCMS: ret. time: 18.89 min.; purity: 83.0%; MS (m/e): 520.97 ( $\text{MH}^+$ ).

15                                **7.3.921    N2,N4-Bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950247)**

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ( $\text{CHCl}_3$ :Acetone, 2:1) to give N2,N4-bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine.  $^1\text{H}$  NMR (MeOD, 300 MHz):  $\delta$  8.58 (d, 1H,  $J = 2.4$  Hz), 6.75-7.53 (m, 8H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 6H), 1.99 (s, 6H); LCMS: ret. time: 21.51 min.; purity: 91.8%; MS (m/e): 563.00 ( $\text{MH}^+$ ).

25                                **7.3.922    N4-(3-Nitrophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950261)**

A mixture of equimolar amounts of 2-chloro-N4-(3-nitrophenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at  $110^\circ\text{C}$  for 24h or in EtOH using microwave at  $175^\circ\text{C}$  for 10-20 min followed by aqueous work up gave N4-(3-nitrophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 92.7%; MS (m/e): 412.94 ( $\text{MH}^+$ ).

**7.3.923 N4-(3-Aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine HCl salt (R950262)**

N4-(3-Nitrophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and Pd/C 10% (50% water content) were suspended in EtOH-10% aqueous HCl (1 : 1) and hydrogenated in a Parr apparatus for 2 hours (22 °C, 50 psi). The suspension was filtered over celite and carefully washed with MeOH. The combined filtrates were concentrated under reduced pressure to give the HCl salt of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.7%; MS (m/e): 383.07 (M-Cl<sup>+</sup>, 100).

**7.3.924 N4-(3-Aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950263)**

The HCl salt of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was neutralized with aqueous sodium carbonate solution and extracted with EtOAc. The organic phase was dried and concentrated to give N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a pale yellow solid. <sup>1</sup>H NMR (DMSO): δ 10.00 (s, 1H), 9.92 (s, 1H), 8.07 (d, 1H, J = 2.4 Hz), 8.15 (bs, 2H), 7.91-8.07 (m, 3H), 7.08-7.21 (m, 5H), 6.56 (d, 1H, J = 7.2 Hz), 4.32 (s, 2H), 2.72 (d, 3H, J = 4.8 Hz); LCMS: purity: 92.7%; MS (m/e): 383.17 (MH<sup>+</sup>, 100).

**7.3.925 N4-(3-Bis-N-methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950264)**

A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of MeI and sodium bicarbonate. The mixture was stirred for 1.5 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-bis-N-methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 90.2%; MS (m/e): 411.04 (MH<sup>+</sup>, 100).

**7.3.926 N4-(3-N-Hydroxyethylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950265)**

A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of 2-bromoethanol and sodium bicarbonate. The mixture was stirred for 16 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-N-hydroxyethylaminophenyl)-5-fluoro. LCMS: purity: 90.2%; MS (m/e): 427.33 (MH<sup>+</sup>, 100).

**7.3.927 N4-(3-Bis(N-hydroxyethyl)aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950266)**

A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of 2-bromoethanol and sodium bicarbonate. The mixture was stirred for 16 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-bis(N-hydroxyethyl)aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 94.2%; MS (m/e): 471.46 (MH<sup>+</sup>, 100).

**7.3.928 N4-(3-N-Methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950267)**

A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of MeI and sodium bicarbonate. The mixture was stirred for 1.5 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-N-methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.3%; MS (m/e): 397.02 (MH<sup>+</sup>, 100).

**7.3.929 N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950290)**

A mixture of equimolar amounts of 2-chloro-N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure

tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 443.20 (MH<sup>+</sup>).

5                                **7.3.930    N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine (R950291)**

The reaction of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (0.1 g) and LiOH (10  
10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave the solid. The resulting solid was filtered, washed with water and dried to give N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 91.5%; MS (m/e): 415.16 (MH<sup>+</sup>).

15                                **7.3.931    N4-(3-Methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950293)**

A solution of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with  
20 a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(3-methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 96.8%; MS (m/e): 457.25 (MH<sup>+</sup>).

25                                **7.3.932    N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950294)**

A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in  
30 EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 92.1%; MS (m/e): 469.26 (MH<sup>+</sup>).